## D. REMARKS

Upon entry of the foregoing amendment, claims 23-34 are pending. Claims 1-22 has been cancelled without prejudice, and claims 23-34 have been added. The fact that Claims 1-22 have been cancelled without prejudice is not be construed as an admission by Applicants or Applicants' attorneys that such claims are not patentable, and Applicants reserves the right to prosecute such claims in a continuing application.

**Rejections under 35 U.S.C. § 102(a)**

The Examiner had rejected claims 1-4 and 21 under 35 U.S.C. § 102(a) as being anticipated by Tempest et al. ("Tempest"). In particular, the Examiner asserts that the Johnson Declaration "does not set forth clearly that there was conception, diligence, and reduction to practice with respect to all limitations taught by Tempest and recited in the instant claims. *See*, Paper No. 23, p. 3, paragraph No. 12. In addition, the Examiner states that "[a]lthough it is noted that the evidence provided in Exhibit 2-4 do involve a neutralizing RSV F antigen antibody, Applicant is invited to clarify the Declaration with respect to the claimed limitation." *See*, Paper No. 23, p. 3, paragraph No. 12.

This rejection is respectfully traversed.

Preliminarily, Applicants respectfully point out that claims 1-22 have been canceled and claims 23-34 have been added to more distinctly claim what applicant regards as the invention. The present invention, as claimed, is directed to a human-murine neutralizing antibody against respiratory syncytial virus which is specific for respiratory syncytial virus F protein.

Applicants note that the Examiner asserts, in Paper No. 23 on page 3, that it is "unclear from the Declaration as filed that the contributions of Ms. Lisa Bennett and Mr. David Pfarr were made under the direction of Dr. Johnson." Applicants respectfully point out that Dr. Johnson testifies in his Declaration that he is the inventor of the

claimed subject matter. In addition, Applicants respectfully point out that Dr. Johnson is the sole inventor of the claimed invention. Therefore, Applicants assert that it is clear that any work by Lisa Bennett and David Pfarr would have been performed under Dr. Johnson's supervision and direction. If, however, the Examiner needs further information to clarify this issue, Applicants will provide a supplemental declaration.

In addition, Applicants respectfully point out that the Examiner asserts the following in Paper No. 23 on page 3: "the Johnson 1.131 Declaration does not clearly set forth that there was conception, diligence, and reduction to practice with respect to all limitations taught by Tempest et al. and recited in the instant claims." The examiner then states that "[a]lthough it is noted that the evidence provided in Exhibit 2-4 do involve a neutralizing RSV F antigen antibody, Applicant is invited to clarify the Declaration with respect to the claimed limitation." *See*, Paper No. 23, p. 3, paragraph No. 12. In response to the Examiner, Applicants respectfully point out that all the previous claims are cancelled and that the new claims recite a neutralizing antibody against respiratory syncytial virus as allegedly disclosed in Tempest and as the Examiner concedes was demonstrated in the Johnson Declaration. Applicants believe that Dr. Johnson's declaration and the attached Exhibits do show conception, diligence and reduction to practice for claims 23-34.

Therefore, in view of the above, Tempest is no longer an effective reference against the claimed invention. It is therefore respectfully requested that the rejection under 35 U.S.C. § 102(a) be withdrawn.

**Rejections under 35 U.S.C. § 103(a)**

**A.** The original claims 1-4 and 22 stood rejected under 35 U.S.C. § 103 as being unpatentable over Tempest et al. in view of Beeler et al. This rejection is respectfully traversed.

As stated hereinabove, the Applicant has demonstrated that Tempest is no longer an effective reference, thus, Tempest cannot be combined with Beeler in order to

render the claimed invention obvious under 35 U.S.C. § 103. Therefore, Applicants respectfully request that this rejection be withdrawn.

**B.** The original claims 1-4 and 22 stood rejected under 35 U.S.C. § 103 as being unpatentable over Jones et al. in view of Beeler et al.

The rejection of the claims is traversed for the reasons described below.

Applicants respectfully point out that the Examiner bears the burden of factually supporting any *prima facie* conclusion of obviousness. Applicants believe that the Examiner has not successfully established *prima facie* case of obviousness. In sum, Applicants believe that (i) the cited references fail to suggest the claimed invention; (ii) the cited references fail to provide the legally required "reasonable expectation of success" to one skilled in the art; and (iii) there would have been no motivation to combine the references cited by the Examiner.

To find obviousness, there must be a reason or suggestion in the art for carrying out the invention other than the knowledge learned from the Applicant's disclosure. *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). The proper inquiry is whether the art suggested the invention at the time the invention was made, and whether the art would have provided one of ordinary skill in the art with a reasonable expectation of success. *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art and not in the Applicant's disclosure. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991) (Emphasis added).

Prior art references may be combined to render an alleged invention obvious under 35 U.S.C. § 103, but teachings of references can be combined only if there would have been some suggestion or incentive to do so. *ACS Hospital Systems, Inc. v. Montefiore Hospital*, 732 F.2d 1572, 1575 (Fed. Cir. 1984). The Federal Circuit has indicated that a *prima facie* case of obviousness requires "objective evidence of record" demonstrating that there is prior art that teaches or suggest combining the asserted

references as proposed. *In re Lee*, 277 F.3d 1338, 1341 (Fed. Cir. 2002). The Court has also made clear that the requirements for a showing of the teaching or motivation to combine prior art references must be "clear and particular. Broad conclusory statements regarding the teaching of multiple references, standing alone, are not evidence." *In re Dembiczak*, 173 F.3d 994, 999 (Fed. Cir. 1999).

Applicants respectfully point out that Jones discloses the substitution of the CDRs from the heavy chain variable region of mouse antibody B1-8, which binds 4-hydroxy-3-nitrophenacetyl caproic acid, also known as NP-cap, for the corresponding CDRs of a human myeloma protein.

Importantly, Jones does not disclose or suggest to one of ordinary skill in the art the use of CDR's with specificity to any RSV antigen. In addition, Jones did not use the CDRs from both the variable heavy and variable light chains. In Jones, only a mouse $V_h$ CDRs were grafted into a human heavy chain framework region. Furthermore, Jones only examined antigen binding, wherein Jones compared the binding of the mouse monoclonal and polyclonal $MV_{np}$ anti-idotypic antibodies. The difference in affinity to the anti-idiotypic antibody only shows that the CDRs has lost certain determinants in the humanized antibody. Also, Jones provides no suggestion that the antibodies of Jones are useful for use in human therapy. Jones, therefore, does not render Applicants' claimed antibodies obvious to one of ordinary skill in the art.

Beeler discloses 18 murine monoclonal antibodies which recognize the F glycoprotein of respiratory syncytial virus (RSV). The antibodies were used to construct a map of epitopes of RSV involved in neutralization and fusion. Beeler, however, does not suggest to one of ordinary skill in the art which, if any, of these antibodies may be modified to provide a human-murine antibody as claimed by Applicants. Therefore, Beeler clearly does not render Applicants' claimed human-murine antibody obvious to one of ordinary skill in the art.

As described above, there is no motivation to combine the Jones and Beeler references. In fact, neither reference discloses or hints the Applicants' claimed human-

murine antibodies to one of ordinary skill in the art. Further, Applicants point out that combining these references does not provide the person with ordinary skill in the art with a reasonable expectation of success, especially for the claimed methods of preventing RSV infection. On the contrary, Jones shows that by grafting the CDRs, the CDRs had lost certain determinants in the humanized antibody. Therefore, for the above stated reasons Applicants respectfully requested that the rejection under 35 U.S.C. § 103 be reconsidered and withdrawn.

**C.** The original claims 1-4 and 22 stood rejected under 35 U.S.C. § 103 as being unpatentable over Queen et al. in view of Beeler et al.

These rejections are respectfully traversed.

Beeler, as stated above, is directed solely to murine monoclonal antibodies. Beeler does not disclose or suggest to one of ordinary skill in the art human-murine antibodies. Furthermore, Beeler does not disclose or suggest to one of ordinary skill in the art humanized antibodies of any kind. Importantly, Beeler does not disclose or suggest to one of ordinary skill in the art which, if any, of the 18 murine monoclonal anti-RSV antibodies disclosed therein could be humanized and retain viral neutralization properties at therapeutically effective levels. Thus, the claimed human-murine antibodies of the present invention are patentable over Beeler.

Queen discloses a humanized antibody which has complementarity determining regions, or CDRs from a donor immunoglobulin, which may, for example, be a mouse or rat immunoglobulin, and heavy and light chain variable region frameworks from human acceptor immunoglobulin heavy and light chain frameworks. The antibody may be an anti-Interleukin-2 receptor antibody, an anti-Herpes Simplex Virus (HSV) antibody, an anti-CD33 antibody, an anti-cytomegalovirus (CMV) antibody, an anti-Interferon-gamma antibody or an anti-Tac antibody. Queen, however, does not disclose or suggest to one of ordinary skill in the art a neutralizing RSV F protein antibody.

Because Beeler is directed only to murine monoclonal antibodies, Beeler adds nothing to the disclosure of Queen. Therefore, the combination of Queen and Beeler does not suggest Applicants' claimed humanized antibody against respiratory syncytial virus to one of ordinary skill in the art. Further, Applicants point out that combing these references does not provide the person with ordinary skill in the art with a reasonable expectation of success, especially for the claimed methods of preventing RSV infection.

In view of the foregoing, the Examiner has failed to establish a *prima facie* case of obviousness. Nonetheless, assuming *arguendo* that the Examiner had established a *prima facie* showing of obviousness of the claimed invention, Applicants respectfully point out that Applicants may rebut such a showing with evidence including secondary considerations such as commercial success and long felt need, but unsolved needs. (*See, Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459, at 467 (Sup. Ct. 1965)). Thus, Applicants submit herewith Exhibits A-E (discussed in detail below) which demonstrate that the claimed invention discovered by Dr. Johnson has not only filled a long felt need in the medical community, but has also been exceptionally commercially successful.

**Exhibits 1-5**

Exhibit 1 is the package insert for an antibody of the present invention manufactured by MedImmune, Inc. (the assignee of the instant application) and sold under the trademark Synagis.® As shown in the Exhibit, Synagis® is a human-murine neutralizing antibody against respiratory syncytial virus which is specific for respiratory syncytial virus F protein. *See*, Exhibit 1, page 1st paragraph.

Exhibit 2 is a press release of January 30, 2003, which states that in 2002, worldwide sales of Synagis® were $668 million, a 29% increase over $516 million in 2001. Exhibit 2 also states that worldwide sales of Synagis® in the fourth quarter of 2002 were $312 million, up 25% from fourth quarter sales of $250 million in 2001.

Exhibit 3 is a press release of July 24, 2003, which states that in the first six months of 2003, worldwide sales of Synagis® were $447 million, a 37% increase over the first six months of 2002.

Exhibit 4 is a Journal article from Pediatrics International (2002) 44: 235-241, entitled "Prevention of respiratory syncytial virus infections in high-risk infants by monoclonal antibody (palivizumab)." This article states that there had been a long felt need for a therapeutically effective neutralizing antibody against respiratory syncytial virus. In particular, on page 235, column one, the author states that "Palivizumab (to be marketed under the trade name Synagis) is the first monoclonal antibody proven to be efficacious for the immunoprophylaxis of an infectious disease in humans." In addition, the last sentence of the abstract states that "in light of the lack of effective vaccines for this serious health risk, palivizumab offers the only option for prophylaxis against RSV disease in high risk infants." Thus, the Synagis antibody, one of the embodiments of the claimed invention, satisfied a long felt medical need.

Exhibit 5 is an article from the Journal of Infection and Chemotherapy (2002) 8: 201-206, entitled "Development and use of palivizumab (Synagis): a passive immunoprophylactic agent for RSV". This articles provides further evidence that the claimed invention has fulfilled a long felt need. In the abstract, the author states that "[t]he first genetically engineered agent to be used effectively against a human infectious agent, palivizumab significantly reduces the number of hospitalization caused by RSV in high-risk infants."

Applicants respectfully point out that Exhibits 1 through 5 demonstrate that the claimed invention has been commercially successful due to the fact that it has generated over a billion dollars in sales over the last couple of years. Further, Applicants point out that there was a long felt need to reduce RSV infection in children. Exhibits 4 and 5 demonstrate that palivizumab has made a significant impact in treating high-risk infants against RSV infection. This, coupled with the commercial success, shows that there had been a long felt need for a therapeutically effective neutralizing antibody against respiratory syncytial virus. Therefore, assuming *arguendo* that the

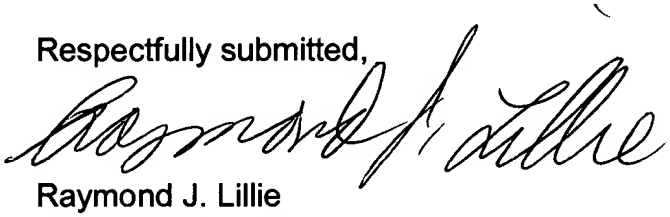
Examiner has established a *prima facie* showing of obviousness of the claimed invention, Applicants have successfully rebutted such a showing with evidence that the claimed invention has been commercially successful and that it has satisfied a long felt, but unsolved need in the medical community.

In sum, Beeler et al., Jones et al, and Queen et al, (or a combination thereof) do not disclose or suggest to one of ordinary skill in the art Applicant's claimed antibody. This, coupled with the secondary considerations mentioned above, clearly indicate that Beeler, Jones and Queen do not render Applicant's antibody as claimed obvious to one of ordinary skill in the art. It is therefore respectfully requested that the rejections under 35 U.S.C. § 103 be withdrawn.

**CONCLUSION**

For the above reasons and others, this application is in condition for allowance, and it is therefore respectfully requested that the rejections be reconsidered and withdrawn and a favorable action is hereby solicited.

Respectfully submitted,



Raymond J. Lillie
Registration No. 31,778

#206449 v1

EXHIBIT 1

# SYNAGIS® (PALIVIZUMAB)
## for Intramuscular Administration

**DESCRIPTION:** Synagis® (palivizumab) is a humanized monoclonal antibody (IgG1κ) produced by recombinant DNA technology, directed to an epitope in the A antigenic site of the F protein of respiratory syncytial virus (RSV). Synagis® is a composite of human (95%) and murine (5%) antibody sequences. The human heavy chain sequence was derived from the constant domains of human IgG1 and the variable framework regions of the $V_H$ genes Cor (1) and Cess (2). The human light chain sequence was derived from the constant domain of Cκ and the variable framework regions of the $V_L$ gene K104 with Jκ-4 (3). The murine sequences were derived from a murine monoclonal antibody, Mab 1129 (4), in a process that involved the grafting of the murine complementarity determining regions into the human antibody frameworks. Synagis® is composed of two heavy chains and two light chains and has a molecular weight of approximately 148,000 Daltons.

Synagis® is supplied as a sterile lyophilized product for reconstitution with sterile water for injection. Reconstituted Synagis® is to be administered by intramuscular injection (IM) only. Upon reconstitution, Synagis® contains the following excipients: 47 mM histidine, 3.0 mM glycine and 5.6% mannitol and the active ingredient, palivizumab, at a concentration of 100 milligrams per mL solution. The reconstituted solution should appear clear or slightly opalescent.

**CLINICAL PHARMACOLOGY:** *Mechanism of Action:* Synagis® exhibits neutralizing and fusion-inhibitory activity against RSV. These activities inhibit RSV replication in laboratory experiments. Although resistant RSV strains may be isolated in laboratory studies, a panel of 57 clinical RSV isolates were all neutralized by Synagis® (5). Synagis® serum concentrations of ≥40 μg/mL have been shown to reduce pulmonary RSV replication in the cotton rat model of RSV infection by 100-fold (5). The in vivo neutralizing activity of the active ingredient in Synagis® was assessed in a randomized, placebo-controlled study of 35 pediatric patients tracheally intubated because of RSV disease. In these patients, Synagis® significantly reduced the quantity of RSV in the lower respiratory tract compared to control patients (6).

*Pharmacokinetics:* In pediatric patients less than 24 months of age without congenital heart disease, the mean half-life of Synagis® was 20 days and monthly intramuscular doses of 15 mg/kg achieved mean ± SD 30 day trough serum drug concentrations of 37 ± 21 μg/mL after the first injection, 57 ± 41 μg/mL after the second injection, 68 ± 51 μg/mL after the third injection and 72 ± 50 μg/mL after the fourth injection (7). Trough concentrations following the first and fourth Synagis® dose were similar in children with congenital heart disease and in non-cardiac patients. In pediatric patients given Synagis® for a second season, the mean ± SD serum concentrations following the first and fourth injections were 61 ± 17 μg/mL and 86 ± 31 μg/mL, respectively.

In 139 pediatric patients ≤24 months of age with hemodynamically significant congenital heart disease (CHD) who received Synagis® and underwent cardio-pulmonary bypass for open-heart surgery, the mean ± SD serum Synagis® concentration was 98 ± 52 μg/mL before bypass and declined to 41 ± 33 μg/mL after bypass, a reduction of 58% (see *DOSAGE AND ADMINISTRATION).* The clinical significance of this reduction is unknown.

Specific studies were not conducted to evaluate the effects of demographic parameters on Synagis® systemic exposure. However, no effects of gender, age, body weight or race on Synagis® serum trough concentrations were observed in a clinical study with 639 pediatric patients with congenital heart disease (≤24 months of age) receiving five monthly intramuscular injections of 15 mg/kg of Synagis®.

**CLINICAL STUDIES:** The safety and efficacy of Synagis® were assessed in two randomized, double-blind, placebo-controlled trials of prophylaxis against RSV infection in pediatric patients at high risk of an RSV-related hospitalization. Trial 1 was conducted during a single RSV season and studied a total of 1502 patients ≤24 months of age with bronchopulmonary dysplasia (BPD) or infants with premature birth (≤35 weeks gestation) who were ≤6 months of age at study entry (7). Trial 2 was conducted over four consecutive seasons among a total of 1287 patients ≤24 months of age with hemodynamically significant congenital heart disease. In both trials participants received 15 mg/kg Synagis® or an equivalent volume of placebo IM monthly for five injections and were followed for 150 days from randomization. In Trial 1, 99% of all subjects completed the study and 93% completed all five injections. In Trial 2, 96% of all subjects completed the study and 92% completed all five injections. The incidence of RSV hospitalization is shown in Table 1.

**Table 1: Incidence of RSV Hospitalization by Treatment Group**

| Trial | | Placebo | Synagis® | Difference between groups | Relative Reduction | p-Value |
|---|---|---|---|---|---|---|
| Trial 1 IMpact-RSV | n | 500 | 1002 | | | |
| | Hospitalization | 53 (10.6%) | 48 (4.8%) | 5.8% | 55% | <0.001 |
| Trial 2 CHD | n | 648 | 639 | | | |
| | Hospitalization | 63 (9.7%) | 34 (5.3%) | 4.4% | 45% | 0.003 |

In Trial 1, the reduction of RSV hospitalization was observed both in patients with BPD (34/266 [12.8%] placebo vs. 39/496 [7.9%] Synagis®), and in premature infants without BPD (19/234 [8.1%] placebo vs. 9/506 [1.8%] Synagis®). In Trial 2, reductions were observed in acyanotic (36/305 [11.8%] placebo vs. 15/300 [5.0%] Synagis®) and cyanotic children (27/343 [7.9%] placebo vs. 19/339 [5.6%] Synagis®).

The clinical studies do not suggest that RSV infection was less severe among RSV hospitalized patients who received Synagis® compared to those who received placebo.

**INDICATIONS AND USAGE:** Synagis® is indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients at high risk of RSV disease. Safety and efficacy were established in infants with bronchopulmonary dysplasia (BPD), infants with a history of premature birth (≤35 weeks gestational age), and children with hemodynamically significant CHD. (see *CLINICAL STUDIES)*

**CONTRAINDICATIONS:** Synagis® should not be used in pediatric patients with a history of a severe prior reaction to Synagis® or other components of this product.

**WARNINGS:** Very rare cases of anaphylaxis (<1 case per 100,000 patients) have been reported following re-exposure to Synagis® (see *ADVERSE REACTIONS, POSTMARKETING EXPERIENCE).* Rare severe acute hypersensitivity reactions have also been reported on initial exposure or re-exposure to Synagis®. If a severe hypersensitivity reaction occurs, therapy with Synagis® should be permanently discontinued. If milder hypersensitivity reactions occur, caution should be used on readministration of Synagis®. **If anaphylaxis or severe allergic reactions occur, administer appropriate medications (e.g., epinephrine) and provide supportive care as required.**

**PRECAUTIONS:** *General:* Synagis® is for intramuscular use only. As with any intramuscular injection, Synagis® should be given with caution to patients with thrombocytopenia or any coagulation disorder.

The safety and efficacy of Synagis® have not been demonstrated for treatment of established RSV disease.

The single-use vial of Synagis® does not contain a preservative. Injections should be given within 6 hours after reconstitution. The vial should not be re-entered. Discard any unused portion.

*Drug Interactions:* No formal drug-drug interaction studies were conducted. In Trial 1, the proportions of patients in the placebo and Synagis® groups who received routine childhood vaccines, influenza vaccine, bronchodilators or corticosteroids were similar and no incremental increase in adverse reactions was observed among patients receiving these agents.

*Carcinogenesis, Mutagenesis, Impairment of Fertility:* Carcinogenesis, mutagenesis and reproductive toxicity studies have not been performed.

*Pregnancy:* Pregnancy Category C: Synagis® is not indicated for adult usage and animal reproduction studies have not been conducted. It is also not known whether Synagis® can cause fetal harm when administered to a pregnant woman or could affect reproductive capacity.

**ADVERSE REACTIONS:**
The most serious adverse reactions occurring with Synagis® treatment are anaphylaxis and other acute hypersensitivity reactions (see *WARNINGS).* The adverse reactions most commonly observed in Synagis®-treated patients were upper respiratory tract infection, otitis media, fever, rhinitis, rash, diarrhea, cough, vomiting, gastroenteritis, and wheezing. Upper respiratory tract infection, otitis media, fever, and rhinitis occurred at a rate of 1% or greater in the Synagis® group compared to placebo (Table 2).

Because clinical trials are conducted under widely varying conditions, adverse event rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information does, however, provide a basis for identifying the adverse events that appear to be related to drug use and a basis for approximating rates.

The data described reflect Synagis® exposure for 1641 pediatric patients of age 3 days to 24.1 months in Trials 1 and 2. Among these patients, 496 had bronchopulmonary dysplasia, 506 were premature birth infants less than 6 months of age, and 639 had congenital heart disease.

**Table 2: Adverse Events Occurring at a Rate of 1% or Greater More Frequently in Patients† Receiving Synagis®(palivizumab)**

| Event | Synagis® (n=1641) n (%) | Placebo (n=1148) n (%) |
|---|---|---|
| Upper respiratory infection | 830 (50.6) | 544 (47.4) |
| Otitis media | 597 (36.4) | 397 (34.6) |
| Fever | 446 (27.1) | 289 (25.2) |
| Rhinitis | 439 (26.8) | 282 (24.6) |
| Hernia | 68 (4.1) | 30 (2.6) |
| SGOT Increase | 49 (3.0) | 20 (1.7) |

†Cyanosis (Synagis® [9.1%]/ placebo [6.9%]) and arrhythmia (Synagis® [3.1%]/placebo [1.7%]) were reported during Trial 2 in congenital heart disease patients.

*Immunogenicity*
In Trial 1, the incidence of anti-Synagis® antibody following the fourth injection was 1.1% in the placebo group and 0.7% in the Synagis® group. In pediatric patients receiving Synagis® for a second season, one of the fifty-six patients had transient, low titer reactivity. This reactivity was not associated with adverse events or alteration in serum concentrations. Immunogenicity was not assessed in Trial 2.

These data reflect the percentage of patients whose test results were considered positive for antibodies to Synagis® in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Synagis® with the incidence of antibodies to other products may be misleading.

*Post-Marketing Experience*

The following adverse reactions have been identified and reported during post-approval use of Synagis®. Because the reports of these reactions are voluntary and the population is of uncertain size, it is not always possible to reliably estimate the frequency of the reaction or establish a causal relationship to drug exposure.

Based on experience in over 400,000 patients who have received Synagis® (>2 million doses), rare severe acute hypersensitivity reactions have been reported on initial or subsequent exposure. Very rare cases of anaphylaxis (<1 case per 100,000 patients) have also been reported following re-exposure (see *WARNINGS).* None of the reported hypersensitivity reactions were fatal. Hypersensitivity reactions may include dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia and unresponsiveness. The relationship between these reactions and the development of antibodies to Synagis® is unknown.

Limited information from post-marketing reports suggests that, within a single RSV season, adverse events after a sixth or greater dose of Synagis® are similar in character and frequency to those after the initial five doses.

**OVERDOSAGE:** No data from clinical studies are available on overdosage. No toxicity was observed in rabbits administered a single intramuscular or subcutaneous injection of Synagis® at a dose of 50 mg/kg.

**DOSAGE AND ADMINISTRATION:** The recommended dose of Synagis® is 15 mg/kg of body weight. Patients, including those who develop an RSV infection, should continue to receive monthly doses throughout the RSV season. The first dose should be administered prior to commencement of the RSV season. In the northern hemisphere, the RSV season typically commences in November and lasts through April, but it may begin earlier or persist later in certain communities.

Synagis® serum levels are decreased after cardio-pulmonary bypass (see *CLINICAL PHARMACOLOGY).* Patients undergoing cardio-pulmonary bypass should receive a dose of Synagis® as soon as possible after the cardio-pulmonary bypass procedure (even if sooner than a month from the previous dose). Thereafter, doses should be administered monthly.

Synagis® should be administered in a dose of 15 mg/kg intramuscularly using aseptic technique, preferably in the anterolateral aspect of the thigh. The gluteal muscle should not be used routinely as an injection site because of the risk of damage to the sciatic nerve. The dose per month = patient weight (kg) x 15 mg/kg ÷ 100 mg/mL of Synagis®. Injection volumes over 1 mL should be given as a divided dose.

*Preparation for Administration:*

- To reconstitute, remove the tab portion of the vial cap and clean the rubber stopper with 70% ethanol or equivalent.
- Both the 50 mg and 100 mg vials contain an overfill to allow the withdrawal of 50 milligrams or 100 milligrams respectively when reconstituted following the directions described below.
- SLOWLY add 0.6 mL of sterile water for injection to the 50 mg vial or add 1.0 mL of sterile water for injection to the 100 mg vial. The vial should be gently swirled for 30 seconds to avoid foaming. DO NOT SHAKE VIAL.
- Reconstituted Synagis® should stand at room temperature for a minimum of 20 minutes until the solution clarifies.
- Reconstituted Synagis® should be inspected visually for particulate matter or discoloration prior to administration. The reconstituted solution should appear clear or slightly opalescent. Do not use if there is particulate matter or if the solution is discolored.
- Reconstituted Synagis® does not contain a preservative and should be administered within 6 hours of reconstitution. Synagis® is supplied in single-use vials. DO NOT re-enter the vial. Discard any unused portion.

To prevent the transmission of hepatitis viruses or other infectious agents from one person to another, sterile disposable syringes and needles should be used. Do not reuse syringes and needles.

**HOW SUPPLIED:** Synagis® is supplied in single use vials as lyophilized powder to deliver either 50 milligrams or 100 milligrams when reconstituted with sterile water for injection.

50 mg vial NDC 60574-4112-1
Upon reconstitution the 50 mg vial contains 50 milligrams Synagis® in 0.5 mL.

100 mg vial NDC 60574-4111-1
Upon reconstitution the 100 mg vial contains 100 milligrams Synagis® in 1.0 mL.

Upon receipt and until reconstitution for use, Synagis® should be stored between 2 - 8°C (35.6 - 46.4°F) in its original container. Do not freeze. Do not use beyond the expiration date.

**REFERENCES:**

1. Press E, and Hogg N. The amino acid sequences of the Fd Fragments of Two Human gamma-1 heavy chains. Biochem. J. 1970;117:641-660.
2. Takahashi N, Noma T, and Honjo T. Rearranged immunoglobulin heavy chain variable region ($V_H$) pseudogene that deletes the second complementarity-determining region. Proc. Nat. Acad. Sci. USA 1984;81:5194-5198.
3. Bentley D, and Rabbitts T. Human immunoglobulin variable region genes - DNA sequences of two Vκ genes and a pseudogene. Nature 1980;288:730-733.
4. Beeler JA, and Van Wyke Coelingh K. Neutralization epitopes of the F Protein of Respiratory Syncytial Virus: Effect of mutation upon fusion function. J. Virology 1989;63:2941-2950.
5. Johnson S, Oliver C, Prince GA, et al. Development of a humanized monoclonal antibody (MEDI-493) with potent in vitro and in vivo activity against respiratory syncytial virus. J. Infect. Dis. 1997; 176:1215-1224.
6. Malley R, DeVincenzo J, Ramilo O, et al. Reduction of Respiratory Syncytial Virus (RSV) in Tracheal Aspirates in Intubated Infants by Use of Humanized Monoclonal Antibody to RSV F Protein. J. Infect. Dis. 1998;178:1555-1561.
7. The IMpact RSV Study Group. Palivizumab, a Humanized Respiratory Syncytial Virus Monoclonal Antibody, Reduces Hospitalization From Respiratory Syncytial Virus Infection in High-risk Infants. Pediatrics 1998;102:531-537.





Manufactured by:
MedImmune, Inc.
Gaithersburg, MD 20878
U.S. Gov't. License No. 1252
(1-877-633-4411)

Co-Marketed by:
ROSS PRODUCTS DIVISION
ABBOTT LABORATORIES INC.
COLUMBUS, OHIO 43215-1724

Rev. date: September 14, 2003
SSP03-166

EXHIBIT 2

MedImmune, Inc.

**FOR IMMEDIATE RELEASE**

*Investor Contact*:
William Roberts
Manager, Investor Relations
MedImmune, Inc.
301-527-4358

*Media Contact*:
Jamie Lacey
Associate Director, Public Relations
MedImmune, Inc.
240-632-4035

http://www.medimmune.com

# MEDIMMUNE REPORTS 2002 FOURTH QUARTER AND YEAR-END RESULTS

*-2002 Total Revenue Increased 37 Percent to a Record $848 Million-*

2002 Highlights

- Worldwide Synagis® (palivizumab) sales up 29 percent to $668 million
- Ethyol® (amifostine) sales exceeded $80 million
  FluMist™ receives favorable recommendation from FDA Advisory Panel
- Positive Phase 3 data for Synagis® in congenital heart disease infants submitted to FDA
- MedImmune Vaccines, Inc. created through $1.6 billion acquisition of Aviron
  Three new preclinical programs in-licensed
  Synagis approved and launched in Japan and Canada
- Construction of new headquarters and FluMist manufacturing facilities initiated
- MedImmune Ventures, Inc. established

**GAITHERSBURG, MD, January 30, 2003** – MedImmune, Inc. (Nasdaq: MEDI) today announced that total revenue for the fourth quarter of 2002 increased 30 percent to $382 million, driving revenue to $848 million for the full year ended December 31, 2002. Revenue growth was due primarily to the continued success of Synagis, the company's flagship product used to prevent respiratory syncytial virus (RSV) in high-risk infants. Worldwide sales of Synagis in 2002 were $668 million, a 29-percent increase over 2001 sales of $516 million. For the 2002 fourth quarter, worldwide sales of Synagis increased 25 percent to $312 million from $250 million in the 2001 period. Sales of Ethyol, the company's first oncology product, exceeded $80 million during 2002 and $25 million in the 2002 fourth quarter. In 2001, MedImmune recorded Ethyol revenues of $20 million and $14 million for the year and fourth quarter, respectively. Other revenue in the fourth quarter of 2002 included $25 million related to compensation for 2002 FluMist manufacturing costs from Wyeth, the company's co-promotion partner for the product.

"We made substantial progress in 2002 toward our long-term goals," stated David M. Mott, chief executive officer. "Product sales increased 36 percent; we completed the acquisition and integration of a vaccine company that provides us with our next potential blockbuster product, FluMist; we completed a successful Phase 3 trial with Synagis in children with congenital heart disease; we added three new programs to our preclinical pipeline; and we broke ground on a number of construction projects, including our new headquarters and research and development facility, as well as a new production facility for FluMist."

Mr. Mott added, "In 2003, we look forward to launching FluMist, moving into Phase 3 with our human papillomavirus vaccine for the prevention of cervical cancer, and taking two programs from our preclinical pipeline forward into clinical trials. We expect to achieve a major financial milestone for MedImmune in 2003 with revenues exceeding $1 billion for the first time, reflecting revenue growth of 24 percent to 30 percent. We also expect our earnings to more than double in 2003."

For the fourth quarter 2002, MedImmune reported net earnings of $85 million, or $0.33 per diluted share. For the year ended December 31, 2002, MedImmune reported a loss of $1.1 billion or $4.40 per share. This loss reflects the impact of a $1.2 billion in-process research and development charge associated with the purchase of MedImmune Vaccines (formerly known as Aviron), as well as the inclusion of MedImmune Vaccines' operations in MedImmune's results as of January 10, 2002. In 2001, MedImmune reported net earnings of $99 million, or $0.45 per diluted share, for the fourth quarter, and $149 million, or $0.68 per diluted share for the year.

Adjusted Results

MedImmune also announced "adjusted" results for 2002, which exclude certain amounts associated with the acquisition of MedImmune Vaccines. MedImmune computes "adjusted" earnings by adding back amounts that are related to the acquisition of MedImmune Vaccines, including: the in-process research and development charge; amortization of intangible assets; compensation expense associated with the assumption and vesting of unvested stock options, retention and severance payments; and amortization of premium on convertible subordinated notes. MedImmune believes the "adjusted" results are more indicative of the underlying trends in the operations of the business, and will continue to provide "adjusted" results in addition to reporting earnings computed in accordance with generally accepted accounting principles (GAAP). The accompanying schedules present the reconciliation from GAAP results to "adjusted" results, with additional details included in the notes to those schedules.

Fourth Quarter Adjusted Earnings

For the 2002 fourth quarter, MedImmune's adjusted net earnings were $92 million, or $0.36 per diluted share.

Gross margins on product sales for the 2002 fourth quarter were 76 percent versus 77 percent in the 2001 fourth quarter, reflecting the cost of additional royalty payments related to domestic Synagis sales in 2002, partially offset by manufacturing cost reductions for Synagis.

Research and development expenses rose to $30 million in the 2002 fourth quarter from $21 million last year. The increases were due largely to the inclusion of MedImmune Vaccines' activities and gaining access to various technologies and intellectual property to advance our pipeline.

Selling, general and administrative costs in the fourth quarter of 2002 increased to $102 million from $67 million in the 2001 period, due primarily to increased co-promotion expenses for Synagis, the acquisition of MedImmune Vaccines, and higher marketing expenses for Synagis and Ethyol.

Other operating expenses in the fourth quarter of 2002 were $26 million compared to $2 million in the fourth quarter last year. In addition to pre-production expenses for FluMist, other operating expenses

included a $13 million charge for the write-off of plasma manufacturing assets due to the outsourcing of CytoGam manufacturing activities.

The number of shares used in computing basic and diluted earnings per share increased by approximately 34 million primarily due to shares issued for the acquisition of MedImmune Vaccines.

Adjusted Earnings for the Year 2002
MedImmune's adjusted earnings for 2002 were $107 million, or $0.42 per diluted share.

Gross margins on product sales for 2002 were 74 percent, down two percentage points from the comparable period last year, largely due to the additional royalty payments in 2002 related to domestic Synagis sales.

Research and development expenses rose to $135 million in 2002 from $83 million in the 2001 year, largely due to the inclusion of MedImmune Vaccines' activities, gaining access to various technologies and intellectual property to advance our pipeline, and the progress of the research pipeline over the course of 2002.

Selling, general and administrative costs in 2002 increased to $287 million from $195 million in the 2001 period due primarily to: the acquisition of MedImmune Vaccines; increased co-promotion expenses for Synagis; higher sales and marketing expenses for Synagis and Ethyol; increases in infrastructure costs to support the growth of the business; and costs associated with the settlement of a contractual dispute.

Other operating expenses in 2002 were $79 million compared to $10 million in the 2001 period, primarily due to costs associated with the manufacture of FluMist and the fixed asset write-off associated with the outsourcing of CytoGam manufacturing activities during the fourth quarter.

Results for the year also reflect approximately $14 million in impairment losses on certain equity investments that were affected by the downward movement in the capital markets during 2002.

The number of shares used in computing basic and diluted earnings per share increased by approximately 33 million primarily due to shares issued for the acquisition of MedImmune Vaccines.

Cash and marketable securities at December 31, 2002 were $1.4 billion compared to $778 million at December 31, 2001, primarily reflecting cash and securities received as a part of the acquisition of MedImmune Vaccines and positive cash flow from operations.

**Looking Ahead in 2003**
The following forward-looking information is being provided as a convenience to investors. The guidance and objectives provided below are projections and assume the continued growth and success of MedImmune's existing business, including sales of Synagis and Ethyol, as well as the approval of FluMist by the FDA in the second quarter of 2003 and the subsequent initiation of sales of FluMist in the U.S. in the second half of 2003 and progress on MedImmune's pipeline. Investors should note that sales of Synagis occur primarily during the fourth and first calendar quarters when RSV is most prevalent in the Northern Hemisphere, and that sales of FluMist are expected to primarily occur in the second half of the year, which is the most common time for yearly influenza vaccinations. The company's quarterly results

are expected to reflect this seasonality for its marketed products. The projections provided here are provided on an "adjusted" basis, except where specifically identified as GAAP. Further, the projections are based upon numerous assumptions, many of which MedImmune cannot control and which may not develop as MedImmune expects. Consequently, actual results may differ materially from the guidance and objectives described herein. Please refer to the Disclosure Notice below.

**Guidance for the year ending December 31, 2003**

Adjusted earnings per diluted share: $0.88 to $0.93 (110% to 121% growth over 2002)

- GAAP earnings per diluted share: $0.84 to $0.89

Total revenue of $1.05 to $1.1 billion (24% to 30% growth over 2002)

- Projected product sales growth: 21% to 25% over 2002
- Projected growth of Synagis: 16% to 20% over 2002
- Projected growth of Ethyol: 20% to 25% over 2002
- Total FluMist revenue (product sales and other revenue from milestones and royalties): $120 million to $140 million

Gross margins: approximately 71% of product sales

- Research and development expense: projected to range from $140 million to $145 million
- Selling, general and administrative: projected to be 32% to 33% of product sales

Other expenses: projected to range from $17 million to $20 million

Tax rate: approximately 37%

**Guidance for the quarter ending March 31, 2003**

- Adjusted earnings per diluted share: $0.40 to $0.43 (38% to 48% growth over 2002)
- GAAP earnings per diluted share: $0.38 to $0.41

Total revenue: $410 million to $425 million (24% to 29% growth over 2002)

**Conference Call & Webcast**

MedImmune is offering a live webcast of a discussion by MedImmune management of its earnings and other business results on Thursday, January 30, 2003 at 8:00 a.m. ET. The live webcast may be accessed on MedImmune's website at www.medimmune.com. A replay of the webcast will also be available via our website until February 6, 2003. An audio replay of the webcast will be available beginning at 11:00 a.m. ET on January 30, 2003 until midnight February 6, 2003 by calling (888) 286-8010. The pass code for the audio replay is 71815.

**About MedImmune**

MedImmune is a leading biotechnology company focused on researching, developing and commercializing products to prevent or treat infectious disease, autoimmune disease and cancer. MedImmune actively markets three products, Synagis® (palivizumab), Ethyol® (amifostine) and CytoGam® (cytomegalovirus immune globulin intravenous (human)), and has additional products in clinical testing. MedImmune employs approximately 1,600 people, is headquartered in Gaithersburg, Maryland, and has additional operations in Frederick, Maryland, as well as Pennsylvania, California, the United Kingdom and the Netherlands. For more information on MedImmune, visit the company's website at www.medimmune.com.

Synagis® is marketed for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus in pediatric patients at high risk of RSV disease, which is prominent in the Northern

Hemisphere from October through May (see full prescribing information at www.medimmune.com). Ethyol® is marketed for the reduction of both cumulative renal toxicity associated with repeated administration of cisplatin in patients with advanced ovarian cancer or non-small cell lung cancer ("NSCLC") and moderate to severe xerostomia in patients undergoing post-operative radiation treatment for head and neck cancer, where the radiation port includes a substantial portion of the parotid (see full prescribing information at www.medimmune.com). CytoGam® is marketed for the prophylaxis against cytomegalovirus disease associated with transplantation of kidney, lung, liver, pancreas, and heart (see full prescribing information at www.medimmune.com). FluMist™ is MedImmune's investigational live attenuated intranasal influenza vaccine currently under review by the U.S. Food and Drug Administration.

*DISCLOSURE NOTICE: The information contained in this document is as of January 30, 2003, and will not be updated as a result of new information or future events. This document contains forward - looking statements regarding MedImmune's future financial performance and business prospects. Those statements involve substantial risks and uncertainties. You can identify those statements by the fact that they contain words such as "anticipate," "believe," "estimate," "expect," "intend," "project" or other terms of similar meaning. Those statements reflect management's current beliefs and are based on numerous assumptions, which MedImmune cannot control and which may not develop as MedImmune expects. Consequently, actual results may differ materially from those projected in the forward - looking statements. Among the factors that could cause actual results to differ materially are: seasonal demand for and continued supply of our principal product, Synagis; whether FluMist receives clearance by the Food and Drug Administration and, if it does, whether it will be successfully launched at a favorable price; availability of competitive products in the market; availability of third-party reimbursement for the cost of our products; effectiveness and safety of our products; exposure to product liability, intellectual property or other types of litigation; foreign currency exchange rate fluctuations; changes in generally accepted accounting principles; growth in costs and expenses; the impact of acquisitions, divestitures and other unusual items; and the risks, uncertainties and other matters discussed in MedImmune's Annual Report on Form 10-K for the year ended December 31, 2001 and in its periodic reports on Forms 10-Q and 8-K filed with the U.S. Securities and Exchange Commission. MedImmune cautions that RSV disease occurs primarily during the winter months; MedImmune believes its operating results will reflect that seasonality for the foreseeable future. MedImmune is also developing several products (including FluMist) for potential future marketing. There can be no assurance that such development efforts will succeed, that such products will receive required regulatory clearance or that, even if such regulatory clearance were received, such products would ultimately achieve commercial success.*

- Tables Follow -

**MedImmune, Inc.**
**Condensed Consolidated Statements of Operations (1)**
*(in thousands, except per share data)*

| | Three Months Ended December 31, | | Year Ended December 31, | |
|---|---|---|---|---|
| | 2002 | 2001 | 2002 | 2001 |
| | (Unaudited) | | | |
| Revenues: | | | | |
| Product sales | $ 348,730 | $ 276,021 | $ 785,961 | $ 579,529 |
| Other revenue | 33,020 | 16,682 | 61,778 | 39,150 |
| | 381,750 | 292,703 | 847,739 | 618,679 |
| Costs and expenses: | | | | |
| Cost of sales | 83,112 | 62,437 | 200,927 | 138,707 |
| Research and development | 33,714 | 21,369 | 144,150 | 82,985 |
| Selling, general and administrative | 105,132 | 66,671 | 299,323 | 194,841 |
| Other operating expenses | 31,918 | 1,937 | 100,029 | 9,606 |
| Acquired in-process research and development | - | - | 1,179,321 | - |
| | 253,876 | 152,414 | 1,923,750 | 426,139 |
| Interest income, net | 10,028 | 7,955 | 40,245 | 35,926 |
| Loss on investment activities | (3,408) | - | (14,074) | - |
| Earnings (loss) before income taxes | 134,494 | 148,244 | (1,049,840) | 228,466 |
| Provision for income taxes | 49,903 | 49,738 | 48,175 | 79,506 |
| Net earnings (loss) | $ 84,591 | $ 98,506 | $ (1,098,015) | $ 148,960 |
| Basic earnings (loss) per share | $ 0.34 | $ 0.46 | $ (4.40) | $ 0.70 |
| Shares used in computing basic earnings (loss) per share | 251,078 | 214,273 | 249,625 | 213,378 |
| Diluted earnings (loss) per share | $ 0.33 | $ 0.45 | $ (4.40) | $ 0.68 |
| Shares used in computing diluted earnings (loss) per share | 255,297 | 220,582 | 249,625 | 220,101 |

Note:
(1) As of January 10, 2002, the company has included the results of operations for MedImmune Vaccines, Inc., formerly Aviron, which was acquired through an exchange offer and merger transaction valued at $1.6 billion.

**MedImmune, Inc.**
**Adjusted Consolidated Statements of Operations (Unaudited)**
*(in thousands, except per share data)*

| | Three Months Ended December 31, 2002 | | | Three Months Ended December 31, 2001 |
|---|---|---|---|---|
| | Historical (1) | Acquisition-related Adjustments (2) | Adjusted | Historical |
| Revenues: | | | | |
| Product sales | $ 348,730 | $ - | $ 348,730 | $ 276,021 |
| Other revenue | 33,020 | - | 33,020 | 16,682 |
| | 381,750 | - | 381,750 | 292,703 |
| Costs and expenses: | | | | |
| Cost of sales | 83,112 | - | 83,112 | 62,437 |
| Research and development | 33,714 | (3,730) (3) | 29,984 | 21,369 |
| Selling, general and administrative | 105,132 | (3,225) (4) | 101,907 | 66,671 |
| Other operating expenses | 31,918 | (6,366) (5) | 25,552 | 1,937 |
| | 253,876 | (13,321) | 240,555 | 152,414 |
| Interest income, net | 10,028 | (466) (6) | 9,562 | 7,955 |
| Loss on investment activities | (3,408) | - | (3,408) | - |
| Earnings before income taxes | 134,494 | 12,855 | 147,349 | 148,244 |
| Provision for income taxes | 49,903 | 5,296 | 55,199 | 49,738 |
| Net earnings | $ 84,591 | $ 7,559 | $ 92,150 | $ 98,506 |
| Basic earnings per share | $ 0.34 | $ 0.03 | $ 0.37 | $ 0.46 |
| Shares used in computing basic earnings per share | 251,078 | | 251,078 | 214,273 |
| Diluted earnings per share | $ 0.33 | $ 0.03 | $ 0.36 | $ 0.45 |
| Shares used in computing diluted earnings per share | 255,297 | | 255,297 | 220,582 |

Notes:

(1) Historical results were prepared in accordance with accounting principles generally accepted in the United States of America and include the results of operations for MedImmune Vaccines, Inc., as of January 10, 2002.

(2) Acquisition-related adjustments are the amounts listed in notes (3) through (6) that are related to the company's acquisition of MedImmune Vaccines, Inc.

(3) Consists of $0.7 million, principally for stock compensation expense for unvested stock options assumed in conjunction with the merger transaction; $1.7 million for retention payments; and $1.3 million for stock compensation expense for acceleration of stock options in connection with a retention plan.

(4) Consists of $2.5 million, principally for amortization of intangible assets and stock compensation expense for unvested stock options assumed in conjunction with the merger transaction; $0.5 million for retention payments; and $0.2 million for stock compensation expense for acceleration of stock options in connection with a retention plan.

(5) Consists of $2.8 million, principally for amortization of intangible assets and stock compensation expense for unvested stock options assumed in conjunction with the merger transaction; $2.2 million for retention payments; and $1.3 million for stock compensation expense for acceleration of stock options in connection with a retention plan.

(6) Consists of $0.5 million, relating to the amortization of premium on MedImmune Vaccines' Convertible Subordinated Notes.

**MedImmune, Inc.**
**Adjusted Consolidated Statements of Operations (Unaudited)**
*(in thousands, except per share data)*

| | Year Ended December 31, 2002 | | | Year Ended December 31, 2001 |
|---|---|---|---|---|
| | Historical (1) | Acquisition-related Adjustments (2) | Adjusted | Historical |
| Revenues: | | | | |
| Product sales | $ 785,961 | $ - | $ 785,961 | $ 579,529 |
| Other revenue | 61,778 | - | 61,778 | 39,150 |
| | 847,739 | - | 847,739 | 618,679 |
| Costs and expenses: | | | | |
| Cost of sales | 200,927 | - | 200,927 | 138,707 |
| Research and development | 144,150 | (9,386) (3) | 134,764 | 82,985 |
| Selling, general and administrative | 299,323 | (11,857) (4) | 287,466 | 194,841 |
| Other operating expenses | 100,029 | (20,815) (5) | 79,214 | 9,606 |
| Acquired in-process research and development | 1,179,321 | (1,179,321) (7) | - | - |
| | 1,923,750 | (1,221,379) | 702,371 | 426,139 |
| Interest income, net | 40,245 | (1,818) (6) | 38,427 | 35,926 |
| Loss on investment activities | (14,074) | - | (14,074) | - |
| (Loss) earnings before income taxes | (1,049,840) | 1,219,561 | 169,721 | 228,466 |
| Provision for income taxes | 48,175 | 14,972 | 63,147 | 79,506 |
| Net (loss) earnings | $(1,098,015) | $1,204,589 | $ 106,574 | $ 148,960 |
| Basic (loss) earnings per share | $ (4.40) | $ 4.83 | $ 0.43 | $ 0.70 |
| Shares used in computing basic (loss) earnings per share | 249,625 | | 249,625 | 213,378 |
| Diluted (loss) earnings per share | $ (4.40) | $ 4.82 | $ 0.42 | $ 0.68 |
| Shares used in computing diluted (loss) earnings per share | 249,625 | | 252,653 | 220,101 |

Notes:

(1) Historical results were prepared in accordance with accounting principles generally accepted in the United States of America and include the results of operations for MedImmune Vaccines, Inc. as of January 10, 2002.

(2) Acquisition-related adjustments are the amounts listed in notes (3) through (7) that are related to the company's acquisition of MedImmune Vaccines, Inc.

(3) Consists of $4.6 million, principally for stock compensation expense for unvested stock options assumed in conjunction with the merger transaction; $1.7 million for retention payments; $1.3 million for stock compensation expense for acceleration of stock options in connection with a retention plan; and $1.8 million relating to retention payments and stock compensation expense for acceleration of stock options for certain executives of the acquired entity.

(4) Consists of $11.1 million, principally for amortization of intangible assets and stock compensation expense for unvested stock options assumed in conjunction with the merger transaction; $0.5 million for retention payments; and $0.2 million for stock compensation expense for acceleration of stock options in connection with a retention plan.

(5) Consists of $13.2 million, principally for amortization of intangible assets and stock compensation expense for unvested stock options assumed in conjunction with the merger transaction; $2.2 million for retention payments; $1.3 million for stock compensation expense for acceleration of stock options in connection with a retention plan; and $4.0 million relating to retention payments and stock compensation expense for acceleration of stock options for certain executives of the acquired entity.

(6) Consists of $1.8 million relating to the amortization of premium on MedImmune Vaccines' Convertible Subordinated Notes.

(7) Represents the fair value of purchased in-process technology of $1.2 billion, primarily related to MedImmune Vaccines' lead product candidate, FluMist, which has not been approved by the FDA.

**MedImmune, Inc.**
**C ndensed Consolidated Balance Sheets (1)**
*(in thousands)*

| | December 31, 2002 | December 31, 2001 |
|---|---|---|
| Assets: | | |
| Cash and marketable securities | $ 1,423,056 | $ 777,690 |
| Trade and contract receivables, net | 124,172 | 127,960 |
| Inventory, net | 59,963 | 52,691 |
| Deferred taxes, net | 247,773 | 163,641 |
| Property and equipment, net | 183,992 | 95,402 |
| Goodwill and intangible assets, net | 129,245 | - |
| Other assets | 20,088 | 19,471 |
| | $ 2,188,289 | $ 1,236,855 |
| Liabilities and shareholders' equity: | | |
| Accounts payable | $ 19,773 | $ 5,873 |
| Accrued expenses | 231,407 | 160,154 |
| Other liabilities | 37,669 | 17,011 |
| Long term debt | 222,206 | 9,544 |
| Shareholders' equity | 1,677,234 | 1,044,273 |
| | $ 2,188,289 | $ 1,236,855 |
| Common shares outstanding | 251,262 | 214,484 |

Note:
(1) Certain prior year amounts have been reclassified to conform to the current presentation.

EXHIBIT 3

Medimmune, Inc.

**FOR IMMEDIATE RELEASE**

*Investor Contacts*:
William Roberts
Senior Manager, Investor Relations
301-527-4358

John Filler
Senior Analyst, Investor Relations
240-632-4086

*Media Contact*:
Jamie Lacey
Associate Director, Public Relations
240-632-4035

http://www.medimmune.com

# MEDIMMUNE REPORTS RECORD REVENUES FOR 2003 SIX-MONTH PERIOD AND SECOND QUARTER

**-Strong Product Sales Growth and Recent FDA Approval of FluMist™ Driving Positive Results-**

2003 Six-Month Highlights

- Total revenues increased 41 percent to $554 million
- Worldwide Synagis® sales increased 37 percent to $447 million
- Ethyol® sales grew 49 percent to $52 million
- Adjusted net earnings more than doubled to $128 million ($0.50 per diluted share); GAAP earnings grew to $123 million ($0.48 per diluted share)
- FluMist™ approved for marketing by the FDA and recommended by Advisory Committee on Immunization Practices
- Formed alliance with Micromet to develop MT103 for B cell lymphoma

**GAITHERSBURG, MD, July 24, 2003** – MedImmune, Inc. (Nasdaq: MEDI) today announced that total revenues for the first six months of 2003 increased 41 percent to $554 million from $393 million in the first six months of 2002. Product sales for the 2003 six-month period grew 37 percent to $518 million, driven primarily by a 37-percent increase in sales of Synagis® (palivizumab) to $447 million and by a 49-percent increase in sales of Ethyol® (amifostine) to $52 million.

MedImmune's total revenues for the 2003 second quarter increased 85 percent to $118 million from $64 million in the 2002 second quarter. Sales of Synagis in the 2003 quarter increased 69 percent to $55 million, while sales of Ethyol grew 49 percent to $25 million. Other revenues for the 2003 second quarter included approximately $28 million in milestone payments for the approval of FluMist™ (influenza virus vaccine live, intranasal) and for exceeding $100 million in end-user sales of Synagis outside the U.S. in a single respiratory syncytial virus (RSV) season.

"What a quarter for the company, and more importantly, what an exciting time in our history," commented David M. Mott, MedImmune's chief executive officer. "The second quarter of 2003 was incredibly productive on all fronts, with Synagis and Ethyol performing well ahead of plan and FluMist receiving marketing approval by the U.S. Food and Drug Administration and favorable recommendations from the Advisory Committee on Immunization Practices. In other parts of the business, we've recently completed an issuance of $500 million of Convertible Notes, and begun a

multi-year stock repurchase program. We also continue to build our pipeline with the recently announced alliance with Micromet, a private German biotechnology company."

For the first six months of 2003, MedImmune reported net earnings of $123 million, or $0.48 per diluted share, computed in accordance with generally accepted accounting principles (GAAP). For the first six months of 2002, MedImmune reported a GAAP net loss of $1.1 billion, or $4.62 per share. The 2002 loss primarily reflects the impact of a $1.2 billion charge for acquired in-process research and development associated with the acquisition of MedImmune Vaccines, Inc. (formerly known as Aviron) in January 2002.

For the second quarter of 2003, MedImmune reported net earnings of $13 million, or $0.05 per diluted share on a GAAP basis. In the 2002 second quarter, MedImmune reported a net loss of $29 million, or $0.12 per share, on a GAAP basis.

Cash and marketable securities at June 30, 2003 were $1.6 billion, up from $1.4 billion at December 31, 2002, primarily due to positive cash flow from the company's ongoing business operations.

Adjusted Results

MedImmune also announced "adjusted" results today, which exclude certain amounts associated with the acquisition of MedImmune Vaccines. MedImmune computes adjusted earnings in both years by adding back amounts that are related to the acquisition of MedImmune Vaccines. In 2003, these amounts included: amortization of intangible assets; compensation expense associated with the assumption and vesting of unvested stock options; retention payments; and amortization of the premium on convertible subordinated notes acquired as a part of the acquisition of MedImmune Vaccines. In 2002, the adjusted amounts also included the acquired in-process research and development charge and severance payments in addition to amounts for the items previously listed. MedImmune believes the adjusted results are more indicative of the underlying trends in the operations of the business, and will continue to provide adjusted results in addition to reporting earnings computed in accordance with GAAP. The accompanying schedules present the reconciliation from GAAP results to adjusted results, with additional details included in the notes to those schedules.

2003 Six Month Adjusted Earnings

For the 2003 first half, MedImmune's adjusted net earnings more than doubled over the 2002 first half to $128 million, or $0.50 per diluted share. In the first six months of 2002, MedImmune's adjusted net earnings were $46 million, or $0.18 per diluted share.

Gross margins on product sales for the 2003 first half were 76 percent compared to 75 percent in the 2002 first half, due to higher margins, particularly for Synagis, which are largely a result of lower sales allowances that increased net product sales.

Research and development (R&D) expenses decreased to $58 million in the 2003 first half from $74 million in the 2002 first half, due largely to the completion of several late-stage clinical trials by the end of 2002, including Phase 2 clinical trials with siplizumab, and the Phase 3 Synagis clinical trial in congenital heart disease patients from which data were submitted to the FDA in December 2002.

Selling, general and administrative (SG&A) costs in the 2003 first half increased to $169 million from $137 million in the 2002 first half, due primarily to increases in co-promotion expenses for Synagis.

Other operating expenses in the 2003 first half were $20 million compared to $33 million in the 2002 first half. The decrease is due to the shift in the costs of FluMist manufacturing that are in inventory this year, but were expensed as other operating costs in the prior year.

MedImmune estimates its effective tax rate to be 37 percent for the 2003 period, compared to 36 percent in the first half of 2002. The increase is largely due to a reduction in the amount of credits available for research and development activities relative to the growth in earnings.

2003 Second Quarter Adjusted Earnings

For the 2003 second quarter, MedImmune's adjusted net earnings increased to $15 million, or $0.06 per diluted share, compared to an adjusted loss of $25 million, or $0.10 per share, for the 2002 second quarter. Gross margins on product sales were 73 percent in both the 2003 and 2002 quarters.

R&D expenses decreased to $28 million in the 2003 second quarter from $33 million in the 2002 second quarter, due largely to the completion of several late-stage clinical trials by the end of 2002, including Phase 2 clinical trials with siplizumab, and the Phase 3 Synagis clinical trial in congenital heart disease patients from which data were submitted to the FDA in December 2002.

SG&A costs in the 2003 second quarter increased to $53 million from $45 million in the comparable 2002 period, due primarily to increased co-promotion expenses for Synagis associated with the product's domestic sales growth and a modest increase in the size of the sales force associated with the marketing launch of FluMist.

Other operating expenses in the 2003 second quarter were $1 million compared to $19 million in the 2002 second quarter. The decrease is due to the shift in the costs of FluMist manufacturing that are in inventory this year, but were expensed as other operating costs in last year's quarter.

**Looking Ahead in 2003**

MedImmune is providing both GAAP and adjusted guidance, as well as a reconciliation between the two, as a convenience to its investors. As previously described in this press release, MedImmune's 2003 adjusted guidance excludes certain amounts associated with the acquisition of MedImmune Vaccines. To reconcile MedImmune's adjusted guidance to its GAAP guidance for 2003, the following acquisition-related expenses should be excluded from the GAAP guidance: approximately $4 million in cost of sales; approximately $2 million in R&D; approximately $9 million in SG&A; and approximately $5 million in other operating expenses. In addition, approximately $2 million of net interest income should be excluded from the GAAP guidance to reconcile to the adjusted guidance. The guidance and objectives provided below are projections and are based upon numerous assumptions, many of which MedImmune cannot control and that may not develop as MedImmune expects. Consequently, actual results may differ materially from the guidance and objectives described in this release. Please refer to the Disclosure Notice below.

**Guidance for the Year Ending December 31, 2003**
MedImmune has increased its 2003 guidance for total revenues, product sales and Synagis sales due to stronger than expected growth in Synagis in the first half of the year. The company also increased its R&D guidance due to costs associated with advancing and expanding the product pipeline. Other than these specifically identified items, all other previously stated financial guidance remains unchanged.

Revenue Guidance for 2003

- Total revenues: $1.1 billion to $1.15 billion (30% to 36% growth over 2002)
  - Product sales: 27% to 31% over 2002
  - Synagis revenues: 23% to 27% over 2002
  - Ethyol revenues: 20% to 25% over 2002
  - Total FluMist revenues (product sales and other revenues, primarily from milestones and royalties): $120 million to $140 million

GAAP Guidance for 2003

- Earnings per diluted share: $0.84 to $0.89 (compared to a 2002 loss of $4.40 per share)
- Gross margins: approximately 71% of product sales
- R&D: $157 million to $162 million
- SG&A: 34% to 35% of product sales
- Other operating expenses: $21 million to $24 million
- Tax rate: approximately 37%

Adjusted Guidance for 2003

- Earnings per diluted share: $0.88 to $0.93 (110% to 121% growth over 2002)
- Gross margins: approximately 71% of product sales
- R&D: $155 million to $160 million
- SG&A: 33% to 34% of product sales
- Other operating expenses: $17 million to $20 million
- Tax rate: approximately 37%

**Guidance for the Quarter Ending September 30, 2003**
For the first time, MedImmune is providing the following guidance for the third quarter of 2003. The difference between the GAAP and adjusted guidance is approximately $3 million of net expenses associated with the acquisition of MedImmune Vaccines.

- Loss per share:
  - Adjusted: ($0.08) to ($0.11)
  - GAAP: $(0.09) to ($0.12)
- Total revenues: $85 million to $95 million

**Conference Call & Webcast**
MedImmune is offering a live webcast of a discussion by MedImmune management of its earnings and other business results on Thursday, July 24, 2003 at 8:00 a.m. Eastern Time. The live webcast may be accessed in the investor section of MedImmune's website, www.medimmune.com. A replay of the webcast will also be available via our website until August 1, 2003. An audio replay of the webcast

will be available, beginning at 11:00 a.m. Eastern Time on July 24, 2003 and ending at midnight August 1, 2003 by calling (888) 286-8010. The pass code for the audio replay is 95451238.

**About MedImmune**
MedImmune is a leading biotechnology company focused on researching, developing and commercializing products to prevent or treat infectious disease, autoimmune disease and cancer. MedImmune actively markets four products, Synagis® (palivizumab), FluMist™ (influenza virus vaccine live, intranasal), Ethyol® (amifostine) and CytoGam® (cytomegalovirus immune globulin intravenous (human)), and has additional products in clinical testing. MedImmune employs approximately 1,700 people, is headquartered in Gaithersburg, Maryland, and has additional operations in Frederick, Maryland, as well as Pennsylvania, California, the United Kingdom and the Netherlands. For more information on MedImmune, visit the company's website at www.medimmune.com.

Synagis is marketed for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus in pediatric patients at high risk of RSV disease, which is prominent in the Northern Hemisphere from October through May. FluMist is marketed for active immunization for the prevention of disease caused by influenza A and B viruses in healthy children and adolescents, 5-17 years of age, and healthy adults, 18-49 years of age. Ethyol is marketed for the reduction of both cumulative renal toxicity associated with repeated administration of cisplatin in patients with advanced ovarian cancer or non-small cell lung cancer and moderate to severe xerostomia in patients undergoing post-operative radiation treatment for head and neck cancer, where the radiation port includes a substantial portion of the parotid. CytoGam is marketed for the prophylaxis against cytomegalovirus disease associated with transplantation of kidney, lung, liver, pancreas, and heart. For full prescribing information of all of MedImmune's products, see the company's website at www.medimmune.com.

*DISCLOSURE NOTICE: The information contained in this document is as of July 24, 2003 and will not be updated as a result of new information or future events. This document contains forward-looking statements regarding MedImmune's future financial performance and business prospects. Those statements involve substantial risks and uncertainties. You can identify those statements by the fact that they contain words such as "anticipate," "believe," "estimate," "expect," "intend," "project" or other terms of similar meaning. Those statements reflect management's current beliefs and are based on numerous assumptions, which MedImmune cannot control and which may not develop as MedImmune expects. Consequently, actual results may differ materially from those projected in the forward-looking statements. Among the factors that could cause actual results to differ materially are: seasonal demand for and supply of Synagis and FluMist; whether FluMist will be successfully launched at a favorable price; availability of competitive products in the market; availability of third-party reimbursement for the cost of our products; effectiveness and safety of our products; exposure to product liability, intellectual property or other types of litigation; foreign currency exchange rate fluctuations; changes in generally accepted accounting principles; growth in costs and expenses; the impact of acquisitions, divestitures and other unusual items; and the risks, uncertainties and other matters discussed in MedImmune's Annual Report on Form 10-K for the year ended December 31, 2002, its quarterly reports on Form 10-Q and its current reports on Form 8-K filed with the U.S. Securities and Exchange Commission. MedImmune cautions that RSV disease and influenza occur primarily during the winter months; MedImmune believes its operating results will reflect that seasonality for the foreseeable future. MedImmune is also developing several products for potential future marketing. There can be no assurance that such development efforts will succeed, that such products will receive required regulatory clearance or that, even if such regulatory clearance were received, such products would ultimately achieve commercial success. This press release contains certain financial measures that are adjusted to exclude amounts required by GAAP, and includes the most directly comparable GAAP measure for each adjusted measure, as well as a reconciliation between the GAAP results and the adjusted results. This press release can be found on MedImmune's website at http://www.medimmune.com in the box marked "News" or with the archived press releases on the Investor Summary page.*

- Tables Follow -

**MedImmune, Inc.**
**Condensed Consolidated Statements of Operations (Unaudited)**
*(in thousands, except per share data)*

| | Three Months Ended June 30, | | Six Months Ended June 30, | |
|---|---|---|---|---|
| | 2003 | 2002 | 2003 | 2002 |
| Revenues: | | | | |
| Product sales | $ 85,864 | $ 57,330 | $ 518,299 | $ 377,998 |
| Other revenue | 31,935 | 6,392 | 35,446 | 15,357 |
| | 117,799 | 63,722 | 553,745 | 393,355 |
| Costs and expenses: | | | | |
| Cost of sales | 23,197 | 15,642 | 126,028 | 95,519 |
| Research and development | 28,904 | 34,545 | 59,568 | 78,614 |
| Selling, general and administrative | 55,495 | 47,354 | 173,581 | 142,994 |
| Other operating expenses | 1,415 | 22,152 | 22,871 | 43,993 |
| Acquired in-process research and development | - | - | - | 1,179,321 |
| | 109,011 | 119,693 | 382,048 | 1,540,441 |
| Interest income, net | 12,706 | 10,096 | 23,897 | 19,268 |
| Loss on investment activities | (139) | (109) | (396) | (109) |
| Earnings (loss) before income taxes | 21,355 | (45,984) | 195,198 | (1,127,927) |
| Provision (benefit) for income taxes | 7,901 | (16,528) | 72,223 | 18,387 |
| Net earnings (loss) | $ 13,454 | $ (29,456) | $ 122,975 | $ (1,146,314) |
| Basic earnings (loss) per share | $ 0.05 | $ (0.12) | $ 0.49 | $ (4.62) |
| Shares used in computing basic earnings (loss) per share | 252,106 | 250,161 | 251,836 | 248,110 |
| Diluted earnings (loss) per share | $ 0.05 | $ (0.12) | $ 0.48 | $ (4.62) |
| Shares used in computing diluted earnings (loss) per share | 258,200 | 250,161 | 257,390 | 248,110 |

**MedImmune, Inc.**
**Selected Financial Information – Reconciliation of GAAP to Adjusted Results (Unaudited)**
*(in thousands, except per share data)*

| | Three Months Ended June 30, 2003 | | | Three Months Ended June 30, 2002 | | |
|---|---|---|---|---|---|---|
| | GAAP (1) | Acquisition-related Adjustments (2) | Adjusted | GAAP (1) | Acquisition-related Adjustments (2) | Adjusted |
| Revenues: | | | | | | |
| Product sales | $ 85,864 | $ - | $ 85,864 | $ 57,330 | $ - | $ 57,330 |
| Other revenue | 31,935 | - | 31,935 | 6,392 | - | 6,392 |
| | 117,799 | - | 117,799 | 63,722 | - | 63,722 |
| Costs and expenses: | | | | | | |
| Cost of sales | 23,197 | - | 23,197 | 15,642 | - | 15,642 |
| Research and development | 28,904 | (1,154) (3) | 27,750 | 34,545 | (1,278) (6) | 33,267 |
| Selling, general and administrative | 55,495 | (2,057) (4) | 53,438 | 47,354 | (2,607) (7) | 44,747 |
| Other operating expenses | 1,415 | - | 1,415 | 22,152 | (3,448) (8) | 18,704 |
| Acquired in-process research and development | - | - | - | - | - | - |
| | 109,011 | (3,211) | 105,800 | 119,693 | (7,333) | 112,360 |
| Interest income, net | 12,706 | (466) (5) | 12,240 | 10,096 | (886) (9) | 9,210 |
| Loss on investment activities | (139) | - | (139) | (109) | - | (109) |
| Earnings (loss) before income taxes | 21,355 | 2,745 | 24,100 | (45,984) | 6,447 | (39,537) |
| Provision for income taxes | 7,901 | 1,016 | 8,917 | (16,528) | 2,281 | (14,247) |
| Net earnings (loss) | $ 13,454 | $ 1,729 | $ 15,183 | $ (29,456) | $ 4,166 | $ (25,290) |
| Basic earnings (loss) per share | $ 0.05 | $ 0.01 | $ 0.06 | $ (0.12) | $ 0.02 | $ (0.10) |
| Shares used in computing basic earnings (loss) per share | 252,106 | | 252,106 | 250,161 | | 250,161 |
| Diluted earnings (loss) per share | $ 0.05 | $ 0.01 | $ 0.06 | $ (0.12) | $ 0.02 | $ (0.10) |
| Shares used in computing diluted earnings (loss) per share | 258,200 | | 258,200 | 250,161 | | 250,161 |

(1) GAAP results are the company's historical results that were prepared in accordance with accounting principles generally accepted in the United States of America and include the results of operations for MedImmune Vaccines, Inc. beginning January 10, 2002.
(2) Acquisition-related adjustments are the amounts listed in notes (3) through (9) that are related to the company's acquisition of MedImmune Vaccines, Inc.
(3) Consists of $0.4 million, principally for stock compensation expense for unvested stock options assumed in conjunction with the merger transaction, $0.3 million for retention payments, and $0.4 million for stock compensation expense for acceleration of stock options in connection with a retention plan.
(4) Consists of $2.1 million, principally for amortization of intangible assets and stock compensation expense for unvested stock options assumed in conjunction with the merger transaction.
(5) Consists of $0.5 million relating to the amortization of premium on MedImmune Vaccines' Convertible Subordinated Notes.
(6) Consists of $1.3 million, principally for stock compensation expense for unvested stock options assumed in conjunction with the merger transaction
(7) Consists of $2.6 million, principally for amortization of intangible assets and stock compensation expense for unvested stock options assumed in conjunction with the merger transaction.
(8) Consists of $3.4 million, principally for amortization of intangible assets and stock compensation expense for unvested stock options assumed in conjunction with the merger transaction.
(9) Consists of $0.9 million relating to the amortization of premium on MedImmune Vaccines' Convertible Subordinated Notes.

**MedImmune, Inc.**
**Selected Financial Information – Reconciliation f GAAP to Adjusted Results (Unaudited)**
*(in thousands, except per share data)*

| | Six Months Ended June 30, 2003 | | | Six Months Ended June 30, 2002 | | |
|---|---|---|---|---|---|---|
| | GAAP (1) | Acquisition-related Adjustments (2) | Adjusted | GAAP (1) | Acquisition-related Adjustments (2) | Adjusted |
| Revenues: | | | | | | |
| Product sales | $ 518,299 | $ - | $ 518,299 | $ 377,998 | $ - | $ 377,998 |
| Other revenue | 35,446 | - | 35,446 | 15,357 | - | 15,357 |
| | 553,745 | - | 553,745 | 393,355 | - | 393,355 |
| Costs and expenses: | | | | | | |
| Cost of sales | 126,028 | - | 126,028 | 95,519 | - | 95,519 |
| Research and development | 59,568 | (2,052) (3) | 57,516 | 78,614 | (4,564) (7) | 74,050 |
| Selling, general and administrative | 173,581 | (4,207) (4) | 169,374 | 142,994 | (5,903) (8) | 137,091 |
| Other operating expenses | 22,871 | (3,164) (5) | 19,707 | 43,993 | (11,018) (9) | 32,975 |
| Acquired in-process research and development | - | - | - | 1,179,321 | (1,179,321) (10) | - |
| | 382,048 | (9,423) | 372,625 | 1,540,441 | (1,200,806) | 339,635 |
| Interest income, net | 23,897 | (932) (6) | 22,965 | 19,268 | (886) (11) | 18,382 |
| Loss on investment activities | (396) | - | (396) | (109) | - | (109) |
| Earnings (loss) before income taxes | 195,198 | 8,491 | 203,689 | (1,127,927) | 1,199,920 | 71,993 |
| Provision for income taxes | 72,223 | 3,142 | 75,365 | 18,387 | 7,354 | 25,741 |
| Net earnings (loss) | $ 122,975 | $ 5,349 | $ 128,324 | $ (1,146,314) | $1,192,566 | $ 46,252 |
| Basic earnings (loss) per share | $ 0.49 | $ 0.02 | $ 0.51 | $ (4.62) | $ 4.81 | $ 0.19 |
| Shares used in computing basic earnings (loss) per share | 251,836 | | 251,836 | 248,110 | | 248,110 |
| Diluted earnings (loss) per share | $ 0.48 | $ 0.02 | $ 0.50 | $ (4.62) | $ 4.80 | $ 0.18 |
| Shares used in computing diluted earnings (loss) per share | 257,390 | | 257,390 | 248,110 | | 254,781 |

(1) GAAP results are the company's historical results that were prepared in accordance with accounting principles generally accepted in the United States of America and include the results of operations for MedImmune Vaccines, Inc. beginning January 10, 2002.
(2) Acquisition-related adjustments are the amounts listed in notes (3) through (11) that are related to the company's acquisition of MedImmune Vaccines, Inc.
(3) Consists of $0.9 million, principally for stock compensation expense for unvested stock options assumed in conjunction with the merger transaction, $0.5 million for retention payments, and $0.7 million for stock compensation expense for acceleration of stock options in connection with a retention plan.
(4) Consists of $4.2 million, principally for amortization of intangible assets and stock compensation expense for unvested stock options assumed in conjunction with the merger transaction.
(5) Consists of $2.7 million, principally for amortization of intangible assets and stock compensation expense for unvested stock options assumed in conjunction with the merger transaction, $0.2 million for retention payments, and $0.2 million for stock compensation expense for acceleration of stock options in connection with a retention plan.
(6) Consists of $0.9 million relating to the amortization of premium on MedImmune Vaccines' Convertible Subordinated Notes.
(7) Consists of $2.8 million, principally for stock compensation expense for unvested stock options assumed in conjunction with the merger transaction, and $1.8 million relating to retention payments and stock compensation expense for acceleration of stock options for certain executives of the acquired entity.
(8) Consists of $5.1 million, principally for amortization of intangible assets and stock compensation expense for unvested stock options assumed in conjunction with the merger transaction, and $0.8 million relating to retention payments and stock compensation expense for acceleration of stock options for certain executives of the acquired entity.
(9) Consists of $7.0 million, principally for amortization of intangible assets and stock compensation expense for unvested stock options assumed in conjunction with the merger transaction, and $4.0 million relating to retention payments and stock compensation expense for acceleration of stock options for certain executives of the acquired entity.
(10) Represents the fair value of purchased in-process technology of $1.2 billion, primarily related to MedImmune Vaccines' lead product candidate, FluMist, which was approved by the FDA on June 17, 2003
(11) Consists of $0.9 million relating to the amortization of premium on MedImmune Vaccines' Convertible Subordinated Notes.

**MedImmune, Inc.**
**C ndensed Consolidated Balance Sheets (1)**
*(in thousands)*

| | June 30, 2003 (*unaudited*) | December 31, 2002 |
|---|---|---|
| Assets: | | |
| Cash and marketable securities | $ 1,587,973 | $ 1,423,056 |
| Trade and contract receivables, net | 40,073 | 124,172 |
| Inventory, net | 81,379 | 59,963 |
| Deferred taxes, net | 185,768 | 247,773 |
| Property and equipment, net | 215,520 | 183,992 |
| Goodwill and intangible assets, net | 120,925 | 129,245 |
| Other assets | 28,387 | 20,088 |
| | $ 2,260,025 | $ 2,188,289 |
| Liabilities and shareholders' equity: | | |
| Accounts payable | $ 12,300 | $ 19,773 |
| Accrued expenses | 149,253 | 231,407 |
| Other liabilities | 38,124 | 41,519 |
| Long term debt | 217,029 | 218,356 |
| Shareholders' equity | 1,843,319 | 1,677,234 |
| | $ 2,260,025 | $ 2,188,289 |
| Common shares outstanding | 252,391 | 251,262 |

(1) Certain prior year amounts have been reclassified to conform to the current presentation.

###

*Pediatrics International* (2002) **44**, 235–241

Review Article

# Prevention of respiratory syncytial virus infections in high-risk infants by monoclonal antibody (palivizumab)

JESSIE R. GROOTHUIS[1] AND HIROSHI NISHIDA[2]

[1]*Abbott Laboratories, Global Medical Affairs, Illinois, USA and* [2]*Neonatal Division, Tokyo Women's Medical College Maternal and Perinatal Center, Tokyo, Japan*

**Abstract** Respiratory syncytial virus (RSV) is a major viral pathogen which causes serious respiratory illness in infants and children worldwide. Palivizumab (Synagis) is an anti-RSV monoclonal antibody administered intramuscularly for the prevention of severe RSV respiratory disease in high-risk infants and young children. The IMpact-RSV trial, the pivotal multicenter, randomized, placebo-controlled trial performed in the USA, Canada and the United Kingdom demonstrated an overall 55% reduction in hospitalization rate due to RSV infection in preterm infants (≤ 35 weeks gestation) with and without chronic lung disease (CLD). Subgroup analysis in premature infants without CLD revealed an even greater reduction in RSV hospitalization rates (78%). Adverse events were infrequent and did not differ between placebo and palivizumab groups. Injection site reactions were infrequent and mild; no differences were observed between palivizumab and placebo subjects. Palivizumab does not interfere with administration of other pediatric vaccines. Comprehensive parent education programs regarding prevention of infection, avoidance of risk factors for infection, careful adherence to infection control policies, and recognition of early symptoms of RSV infection remain important components of RSV prevention strategies. In light of the lack of effective vaccines for this serious health risk, palivizumab offers the only option for prophylaxis against RSV disease in high-risk infants.

**Key words** high-risk infant, palivizumab, prematurity, respiratory syncytial virus, Synagis.

Respiratory illness is reported to be the most frequent cause of rehospitalization of preterm infants, and respiratory syncytial virus (RSV) is the most common cause of viral respiratory infection, illness and hospitalization in this group.[1,2] Years of research have failed to yield a safe and effective RSV vaccine. However, using genetic engineering technology, a humanized monoclonal antibody, palivizumab, has been developed that binds to the RSV fusion (F) protein and neutralizes the virus. Palivizumab (to be marketed under the trade name Synagis) is the first monoclonal antibody proven to be efficacious for the immunoprophylaxis of an infectious disease in humans. The results of the IMpact-RSV trial, a large phase III, randomized, placebo-controlled trial conducted in the USA, Canada, and the United Kingdom, demonstrated an overall 55% reduction in hospitalization due to RSV infection in high-risk infants prophylaxed with palivizumab.[3] The indications for palivizumab use are largely based on this trial. Bridging safety and pharmacokinetic studies on palivizumab were also conducted and the results validate the IMpact-RSV trial findings in Japanese patients. A group of Japanese pediatricians, neonatologists, and infectious disease specialists with particular expertise in the management of RSV infections and high-risk infants have collaborated to define usage guidelines for palivizumab. In the course of the collaboration, these physicians: (i) reviewed the scientific evidence serving as the basis for the clinical use of humanized monoclonal antibody in the immunoprophylaxis of RSV infections; (ii) shared local and overseas experience and practice patterns in the treatment of RSV infection; and (iii) formulated recommendations for the use of palivizumab. This paper summarizes the background information available on RSV and palivizumab, and presents the consensus of the collaborating physicians regarding recommendations for use of palivizumab in high-risk infants and children in Japan. Similar recommendations have been issued in the USA by the American Academy of Pediatrics and by other consensus groups worldwide.[4–6]

Correspondence: Jessie R Groothuis MD, Medical Director, Immunology Global Medical Affairs, Building AP30-2, Abbott Laboratories, 200 Abbott Park Road, Abbott Park Illinois, 60064-6149, USA. Email: Jessie.Groothuis@abbott.com

Received 6 September 2001.

## Background

### RSV

Morris *et al.* isolated a virus causing coryza from chimpanzees in 1956 and named it chimpanzee coryza agent (CCA).[7] Chanock *et al.* isolated comparable viruses from children with pneumonia and laryngotracheobronchitis which formed syncytia in tissue culture and were virtually indistinguishable from CCA.[8] The virus was renamed respiratory syncytial virus (RSV), and it has proven to be a major cause of severe respiratory illness in infants and children worldwide.

Respiratory syncytial virus is a single-stranded RNA virus encoding for 10 proteins. In terms of infectivity and immunogenicity, the most important proteins are the two surface glycoproteins. G and F. The G protein mediates viral attachment to host respiratory epithelial cells, while the F protein mediates viral penetration into the respiratory epitheilial cell and subsequent spread to adjacent cells through fusion of cell membranes and formation of syncytia.[9] Respiratory syncytial virus has two subtypes, A and B, and numerous strains. The F protein is highly conserved within all RSV strains, both temporally and geographically, while the G protein exhibits broad heterogeneity.[10]

### The burden of RSV disease

Respiratory syncytial virus is the most common cause of bronchiolitis and pneumonia in infants and children.[11] It is estimated that RSV accounts directly or indirectly for 600 000–1 000 000 deaths annually in children under 5 years of age worldwide.[12]

In Japan, RSV epidemics occur annually, beginning from October to December, peaking between November and February, and declining from March to May. More than 40% of outpatients are infected with RSV during the peak of the epidemic (Y Takeuchi, pers. comm., 2000). Greater than 25% of RSV hospitalization cases may occur in the summer months.[13] In a study conducted in northern Japan, Saijo *et al.* investigated the incidence of RSV in children up to 13 years of age hospitalized for lower respiratory tract infection (LRTI) from April 1991 to March 1992.[13] In the 317 patients evaluated, 70.5% of children less than 2 years of age were RSV positive. The RSV positive cases accounted for 42.4% of bronchopneumonias, 64.1% of bronchiolitis in all ages, and 74.1% of bronchiolitis in infants less than 12-months-old. At the peak of the season, 64.7% of all cases were RSV-antigen positive.

Saijo *et al.* continued their study for a second year.[14] During the 2-year study period, 162 children under 3 years of age were hospitalized with acute bronchiolitis; 76.5% were RSV-antigen positive, and 43.5% of patients with acute RSV bronchiolitis were 6-months-old or less. The average age of RSV bronchiolitis patients was 11.2 months. The male:female ratio was 1.1:1.0.[14]

Prematurity, defined in Japan as less than or equal to 37 weeks' gestation, has been identified as the major risk factor for severe RSV disease. The premature birth rate in 1999 in Japan was 5.4% of the total birth rate.[15] This relatively low rate may be attributed to several factors, including more consistent prenatal care, a more homogeneous population, and less (but increasing) use of *in vitro* fertilization (IVF) procedures. As the use of IVF procedures increases, the prematurity rate in Japan may rise. There is a greater than 80% survival rate for infants born less than 1000 g (extremely low-birthweight, ELBW (WHO criteria)) in Japan's major neonatal intensive care institutions. Consequently, there is significant morbidity for these infants, including respiratory illness (mainly chronic lung disease (CLD)). In a national survey of ELBW infants born in 1990, at 3 years of age, 3.8% of the children were on home oxygen therapy and 10.9% had recurrent respiratory infection.[16]

Several factors contribute to severe RSV disease in preterm infants. Maternal IgG antibodies cross the placenta in the final weeks of gestation and provide protection for a full-term newborn against RSV disease. However, in the infant born prematurely, these antibodies do not achieve protective levels.[17,18] Anatomically small airways predispose these infants to bronchial obstruction. Premature infants also have poorly developed cellular immunity, which is important for viral clearance from the lungs. Chronic lung disease (formerly designated bronchopulmonary dysplasia), a frequent complication of prematurity, combined with barotrauma and high oxygen concentrations, results in limited pulmonary reserve and an increased susceptibility to serious RSV illness.[19] Additional children at risk to develop severe RSV disease include those with other forms of CLD,[20] congenital heart disease,[21] and immunodeficiency,[22] such as congenital severe combined immunodeficiency, AIDS, HIV infection or resulting from chemotherapy or organ transplantation. Selection of infants who will derive the greatest benefit from immunoprophylaxis necessitates the identification of those infants with underlying physical and demographic factors that place them at greatest risk of hospitalization and/or mechanical ventilation if infected with RSV.

Several recently published studies suggest that there is an association between RSV bronchiolitis in infancy and the development of reactive airway disease later in life. The Tucson Children's Respiratory Study reported increased risk for frequent wheezing (odds ratio (OR) 3.2) and infrequent wheezing (OR 4.3) following mild RSV lower respiratory tract infection (not requiring hospitalization) up to age 11. The risk decreased with age and was not statistically significant by age 13.[23]

Sigurs *et al.* prospectively followed 47 infants hospitalized for RSV bronchiolitis and 93 matched controls for incidence of subsequent asthma.[24] At the age of 7 years, the cumulative prevalence of asthma was 30% in the RSV group versus 3% in the control group ($P < 0.001$). The incidence of recurrent asthma was 23% in the RSV group and 2% in the control group ($P < 0.001$).

## Prevention

Options for treatment of severe RSV lower respiratory tract infection are limited and often controversial.[25] Ribavirin, an antiviral agent approved overseas for RSV, has questionable efficacy and many concerns are associated with its use. Bronchodilators, an obvious choice in obstructive airway disease, have not uniformly proven to be beneficial. Corticosteroids are a theoretical option to treat the inflammatory aspects of RSV disease, but clinical trials have not demonstrated efficacy and the potential toxicity of this treatment approach makes it unacceptable. Therefore, therapy for RSV lower respiratory tract disease is mainly supportive care, including supplemental oxygen, fluids, careful monitoring and ventilation in the most severe cases. Prevention, rather than treatment of severe RSV disease, is the preferred approach, particularly in high-risk infants and young children.

### Vaccines

Prevention of RSV disease in small infants has been problematic and the development of a vaccine to RSV has thus far been unsuccessful. Obstacles to RSV vaccine development include the following:

1 The risk of infection is highest for the very young infant (< 6 months of age). Immunization would therefore be necessary almost immediately after birth, at which time the immune system is still immature. Both the RSV F and G proteins (the epitopes that elicit neutralizing antibody formation) are glycoproteins that are weakly immunogenic in early infancy.
2 Circulating maternal antibody, if present, would neutralize live attenuated RSV vaccine before the infant had the opportunity to mount an immune response.
3 Natural immunity against RSV is short-lived and often does not protect against recurrence of infection, even in individuals with healthy, mature immune systems. Therefore, repeated boosters would most likely be necessary.
4 The existence of two subtypes and multiple strains of RSV makes it difficult to prepare a vaccine that would afford broad protection. A likely vaccine candidate would need to contain both F and G proteins.
5 Experience with a formalin-inactivated vaccine in the 1960s resulted in enhanced RSV pulmonary disease severity in very young vaccinees and raised serious safety concerns.[26] These concerns have not yet been resolved.

### Passive prophylaxis

Administration of both standard and hyperimmune polyclonal immune globulin has been investigated for the prevention of RSV disease. In clinical trials conducted in the late 1980s, standard immune globulin was administered monthly to high-risk infants during the RSV season. There were no major side-effects and a trend towards a reduction in hospital days was observed. However, no statistically significant decrease in the severity of RSV disease was seen. This observation was attributed to insufficient anti-RSV antibody concentrations present in standard immune globulin.[27,28] Subsequently, a hyperimmune RSV polyclonal globulin (RSV-immunoglobulin intravenous (IGIV), RespiGam) was developed. Five infusions of RSV-IGIV given at monthly intervals were administered during the RSV season to preterm infants in two multicenter, randomized controlled trials. The results demonstrated a 41 to 63% reduction in RSV-related hospital admissions.[29,30] Despite a favorable safety and efficacy profile, a number of drawbacks were associated with RSV-IGIV usage. These included:

1 Difficulty of administration (i.v.)
2 Large fluid load (15 mL/kg)
3 High protein load (750 mg/kg)
4 Theoretical risk of transmitting blood-borne pathogens
5 Supply shortages
6 Need to postpone live vaccines (e.g. measles/mumps/rubella, varicella).

A trend towards increased mortality rates was observed in children with cyanotic congenital heart disease (CHD) who had received RSV-IGIV.[29,31] Consequently, administration of RSV-IGIV to infants with complex CHD is contraindicated. Currently, availability of RSV-IGIV is extremely limited and its use has been superseded by palivizumab.

The observation that anti-RSV neutralizing antibodies were effective in preventing serious RSV disease provided the proof of principle that led to the development of RSV-specific monoclonal antibodies. The nasal mucosa is the portal of entry for RSV. Hence, it was thought that protection might be obtained by applying anti-RSV IgA antibody topically. A murine anti-RSV IgA antibody was developed, however, a large phase III studies failed to demonstrate efficacy.[32]

Two separate $IgG_1$ monoclonal antibodies have been developed. The first, SB 209763, is an $IgG_1$ directed against the C epitope of the RSV F protein. A large, multicenter, placebo-controlled clinical trial, in which more than 800 children in the USA and Europe received 10 mg/kg monthly, failed to demonstrate a statistically or clinically significant reduction in RSV-related hospitalizations. This failure was

attributed to two factors: lack of potency and insufficient dose.[33,34]

The second $IgG_1$ monoclonal antibody, palivizumab, is also directed against the RSV F protein, but to a different epitope (A). In a large, double-blind, randomized, placebo-controlled trial (IMpact-RSV), five monthly intramuscular (i.m.) injections of 15 mg/kg palivizumab or placebo were administered to 1502 premature infants with or without CLD during the RSV season.[3] Hospitalizations due to RSV disease (the primary end-point) were reduced by 55% in the palivizumab group ($P < 0.001$). There were no significant differences between palivizumab and placebo groups in the frequency and/or type of adverse events.

#### *Palivizumab*

##### *Mechanisms of action*

Two RSV surface glycoproteins elicit a neutralizing antibody response, G and F proteins. The G protein, responsible for viral attachment to the respiratory endothelial cell, is a poor candidate for development of a monoclonal antibody because of its heterogeneity between the major RSV subtypes, A and B. Conversely, the F protein, responsible for viral fusion with the cell and formation of syncytia, is well conserved between RSV strains, over time and geography.[10] Palivizumab is a humanized monoclonal antibody directed against the RSV F protein A epitope. Its neutralizing activity prevents RSV from fusing with the respiratory endothelial cell membrane, thereby preventing replication.[35] Palivizumab is a recombinant monoclonal antibody, hence it is not derived from pooled human immune globulin. It is free of potential contamination by infectious agents and can be produced in large batch lots, ensuring adequate supply.

##### *Pharmacokinetics*

Dosing studies performed first in the cotton rat suggested that trough palivizumab serum concentrations of 25–30 μg/mL resulted in a mean of >99% reduction of RSV titers in the lungs.[36,37] In previous studies with RSV-IGIV, this 99% reduction correlated well with human protection.[29,30] Based on this paradigm, the dosage of 15 mg/kg was selected. Because the average serum half-life of palivizumab was found to range between 18 and 21 days, palivizumab is dosed every 28–30 days to maintain adequate trough serum concentrations throughout the RSV season.[35]

A pharmacokinetic study was performed in Japanese adults to obtain safety data on palivizumab prior to proceeding with phase I/II studies in pediatric patients.[38] Six Japanese and six overseas healthy adult volunteers were administered palivizumab 3 mg/kg i.m., 3 mg/kg i.v., 10 mg/kg i.v. and 15 mg/kg i.v. In this study, palivizumab was administered intravenously rather than intramuscularly in some cases due to the large volume of the dose required for an adult. Previous studies had established similar pharmacokinetic profiles for both routes of administration.[37] There were no significant differences in maximum concentration achieved, area under the curve (AUC), half-life, clearance and trough concentrations between the Japanese and overseas adult groups. A phase II study was conducted in which 31 infants, 19 with prematurity and 13 with CLD, were given 15 mg/kg per dose of palivizumab intramuscularly. Mean trough levels, serum concentrations and AUC were comparable between the Japanese and overseas infants.[38] Adverse reactions were low and comparable to overseas infants. No significant local reactions were observed.

##### *Binding to RSV isolates*

There is a theoretical possibility that RSV strains exist that have genetic variation in the A epitope of the F protein. If this were the case, palivizumab would not bind to such strains, and therefore, would fail to provide protection against infection with these strains. More than 700 RSV isolates have been collected from 19 countries and tested for their ability to bind palivizumab. A subset of these has also been tested for the ability of palivizumab to neutralize the virus. Palivizumab bound to and neutralized all isolates tested.[39] An additional 23 isolates were collected in Japan, 13 of subtype A and 10 of subtype B. These isolates were tested for their ability to bind palivizumab; all bound the antibody (T Tsutsumi, pers. comm., 2000).

## Article reviews and results

#### *Clinical efficacy of palivizumab*

The efficacy of palivizumab was established in a large, multicenter, double-blind, randomized clinical trial (IMpact-RSV).[3] A total of 139 centers in the USA, Canada and the United Kingdom participated. The trial was conducted during the RSV season in 1996–1997. Infants and children were eligible to enrol if they were: (i) 35 weeks' gestation or less and 6 months of age or younger at the start of the RSV season or (ii) 24-months-old or younger and had a clinical diagnosis of CLD requiring medical treatment (i.e. supplemental oxygen, steroids, bronchodilators, or diuretics) within 6 months of RSV season onset.

A total of 1502 children were randomized in a 2:1 ratio between the palivizumab (1002) and placebo (500) groups. This large sample size allowed for subgroup analysis at trial conclusion. Risk factors and demographics were well balanced between treatment groups. Children received i.m. injections of either 15 mg/kg palivizumab or placebo every

30 days, commencing at the start of the RSV season, for a total of five doses.

Administration of palivizumab resulted in a 55% overall reduction in RSV-related hospitalization, which was the primary end-point (10.6 to 4.8% in placebo *vs* palivizumab, $P < 0.001$). Most secondary end-points were also achieved. Hospital days per 100 children were decreased from 62.6 in the placebo group to 36.4 in the palivizumab group ($P < 0.001$). Oxygen requirement per 100 children was reduced from 50.6 days in the placebo group to 30.3 days in the palivizumab group ($P < 0.001$). The number of days with a LRTI score of 3 days or greater was also reduced (47.4 days *vs* 29.6 days, $P < 0.001$). The incidence of intensive care unit admission was lower in the palivizumab group ($P = 0.026$). There were no differences in hospital course or mechanical ventilation days once RSV disease was established. Incidence of otitis media was similar between treatment groups. There were no differences between groups in incidence or total days of respiratory hospitalization due to non-RSV respiratory viruses. No significant differences were observed in either the types or rates of adverse events or in antipalivizumab antibody formation between palivizumab and placebo groups.

#### *Subgroup analysis*

Palivizumab reduced the hospitalization rates of clinical RSV illness in all subgroups evaluated.[3] Preterm infants without CLD had a 78% reduction in hospitalization (8.1% placebo *vs* 1.8% palivizumab, $P < 0.001$). Preterm infants with CLD had a 39% reduction (12.8% placebo *vs* 7.9% palivizumab, $P = 0.038$).

#### *Post-marketing/phase IV data*

Pharmacovigilance using large numbers of patients in phase IV trials facilitates the expansion of the efficacy and safety profile of new drugs. Palivizumab received marketing approval by the USA Food and Drug Administration in July 1998 and by the European Commission for Proprietary Medicinal Products in August 1999. Numerous postmarketing/phase IV studies have been conducted to collect additional safety and efficacy data on palivizumab. In the USA, the RSV Education and Compliance Helpline (REACH) program was implemented to enhance parent education about RSV and compliance with monthly prophylaxis.[40] Telephone contacts were made bi-monthly and reported adverse events were collected and monitored for follow-up. Despite active collection of adverse event information, a significantly lower rate of reported serious adverse events (SAE) was observed when compared with the IMpact-RSV trial; total rate of children with one or more SAE was 2.8% for REACH, 29.7% for IMpact-RSV palivizumab group, and 34.0% for IMpact-RSV placebo group. The most common SAE included cough, rhinitis, and lung disorder. The hospitalization rate in this cohort was only 1.5%, which compares favorably to the IMpact-RSV rate of 4.8% in palivizumab recipients.

Outcomes studies were conducted in the USA over two consecutive years in which 12 geographically distinct sites evaluated children less than 2-years-old that had received one or more injections of palivizumab.[41,42] The RSV hospitalization rate in the 1839 and 2830 children studied was 2.3 and 2.4%, respectively. In the second year of this study, 45.6% of the children hospitalized had a history of CLD, 11 (0.4%) required intensive care, and 13 (0.46%) required mechanical ventilation.

An Expanded Access program was conducted in 97 centers in 20 countries around the world where palivizumab was not yet available. The adverse events observed in the 665 children enrolled included mild injection site reaction, fever, diarrhea, nervousness, rhinitis and increased cough; the rate observed was less than or equal to that in the IMpact-RSV palivizumab group.[43]

## Conclusion

Respiratory syncytial virus is an important cause of serious lower respiratory tract infection in high-risk infants and young children in Japan. It should be stressed that a major aspect in the prevention of RSV infection in high-risk infants is education of parents and caregivers to reduce exposure and transmission of the virus. Hand washing in all settings, as well as limiting exposure to high-risk settings (e.g. day-care centers) and environmental toxins, such as cigarette smoke, are important preventative measures, particularly during the RSV season. Currently, there is no alternative product to palivizumab for RSV prophylaxis. Palivizumab is currently being considered for licensure for prophylaxis against severe RSV illness in selected high-risk children in Japan.

## Acknowledgments

We appreciate the help and support of Professor Y Takeuchi (Department of Pediatrics, Kawasaki Municipal Hospital), Professor M Fujimura (Department of Neonatal Medicine, Osaka Medical Center and Research Institute for Maternal and Child Health), Professor Y Ogawa (Department of Pediatrics, Saitama Medical Center), and Dr H Tsutsumi (Department of Pediatrics, Sapporo Medical University). We thank Ms Stacy Simpson (Abbott Laboratories) for editorial assistance in the preparation of this manuscript.

## References


1 Cunningham CK, Macmillan JA, Gross SJ. Rehospitalization for respiratory illness in infants of less than 32 weeks' gestation. *Pediatrics* 1991; **88**: 527–32.

2 Yüksel B. Greenough A. Birth weight and hospital readmission of infants born prematurely. *Arch. Pediatr. Adolesc. Med.* 1994; **148**: 384–8.

3 The IMpact RSV Study Group. Reduction of respiratory syncytial virus hospitalization among premature infants and infants with bronchopulmonary dysplasia using respiratory syncytial virus monoclonal antibody prophylaxis. *Pediatrics* 1998; **102**: 531–7.

4 American Academy of Pediatrics Committee on Infectious Diseases. Prevention of respiratory syncytial virus infections: indications for the use of palivizumab and update on the use of RSV-IVIG. *Pediatrics* 1998; **102**: 1211–16.

5 Meissner HC. Welliver RC, Chartrand SA *et al.* Immunoprophylaxis with palivizumab, a humanized respiratory syncytial virus monoclonal antibody, for prevention of respiratory syncytial virus infection in high risk infants: a consensus opinion. *Pediatr. Infect. Dis. J.* 1999; **18**: 223–31.

6 Carbonell-Estrany X, Giuffré L, Kimpen JLL *et al.* Guidelines for the use of Synagis® (palivizumab), a humanized monoclonal antibody, for the prevention of respiratory syncytial virus (RSV) disease in high-risk infants: a consensus opinion. *Infect. Med.* 1999; **16**: 29–33.

7 Morris JA. Blount RE Jr, Savage RE. Recovery of cytopathogenic agent from chimpanzees with coryza. *Proc. Soc. Exp. Biol. Med.* 1956; **92**: 544–9.

8 Chanock RM. Roizman B, Myers R. Recovery from infants with respiratory illness of virus related to chimpanzee coryza agent (CCA). I. Isolation, properties and characterization. *Am. J. Hyg.* 1957; **66**: 281–90.

9 Hall CB. McCarthy CA. Respiratory syncytial virus. In: Mandell GL. Bennett JE, Dolin R (eds). *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 4th edn. Churchill Livingstone, New York, 1995; 1501–19.

10 Garcia-Barreno B, Palomo C, Penas C, Delgado T, Perez-Brena P, Melero JA. Marked differences in the antigenic structure of human respiratory syncytial virus F and G glycoproteins. *J. Virol.* 1989; **63**: 925–32.

11 Hall CB. Respiratory syncytial virus. In: Feigin RD, Cherry JD (eds). *Textbook of Pediatric Infectious Diseases*. WB Saunders Co. Philadelphia, 1998; 2084–111.

12 Simoes EAF. Rieger CHL. RSV infection in developed and developing countries. *Infect. Med.* 1999; **16**: 11–17.

13 Saijo M, Ishii T, Kokubo M, Takimoto M, Takahashi Y. Respiratory syncytial virus infection in lower respiratory tract and asthma attack in hospitalized children in North Hokkaido, Japan. *Acta. Paediatr. Jpn.* 1993; **35**: 233–7.

14 Saijo M, Takahashi S, Kokubo M *et al.* The role of respiratory syncytial virus in acute bronchiolitis in small children in northern Japan. *Acta. Paediatr. Jpn.* 1994; **36**: 371–4.

15 Ministry of Health. The main statistics of maternal and child health. Maternal and Child Health Division, Children and Families Bureau. The Ministry of Health and Welfare, Tokyo, 2000.

16 Nakamura H. Uetani Y, Yoshimoto S *et al.* The results of national survey on prognosis of extremely low birth weight (ELBW) infants at the age of 6. *Nippon Shonika Gakkai Zasshi* 1999; **103**: 998–1006.

17 Glezen WP, Paredes A, Allison JE, Taber LH, Frank AL. Risk of respiratory syncytial virus for infants from low-income families in relationship to age, sex ethnic group, and maternal antibody level. *J. Pediatr.* 1981; **98**: 708–15.

18 de Sierra TM, Kumar ML, Wasser TE, Murphy BR, Subbarao EK. Respiratory syncytial virus-specific immunoglobulins in preterm infants. *J. Pediatr.* 1993; **122**: 787–91.

19 Groothuis JR, Gutierrez KM, Lauer BA. Respiratory syncytial virus infection in children with bronchopulmonary dysplasia. *Pediatrics* 1988; **82**: 199–203.

20 Abman SH, Ogle JW, Butler-Simon N, Rumack CM, Accurso FJ. Role of respiratory syncytial virus in early hospitalizations for respiratory distress of young infants with cystic fibrosis. *J. Pediatr.* 1988; **113**: 826–30.

21 MacDonald NE, Hall CB, Suffin SC, Alexson C, Harris PJ, Manning JA. Respiratory syncytial viral infections in infants with congenital heart disease. *N. Engl. J. Med.* 1982; **307**: 397–400.

22 Harrington RD, Hoonton TM, Hackman RC *et al.* An outbreak of respiratory syncytial virus in a bone marrow transplant center. *J. Infect. Dis.* 1992; **165**: 987–93.

23 Stein RT, Sherrill D, Morgan WJ *et al.* Respiratory syncytial virus in early life and the risk of wheeze and allergy by age 13 years. *Lancet* 1999; **354**: 541–5.

24 Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B. Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7. *Am. J. Respir. Crit. Care Med.* 2000; **161**: 1501–7.

25 Ariagno RL, Groothuis JR, Kimpen JLL. Treatment and prevention of respiratory syncytial virus disease. *Infect. Med.* 1999; **16**: 18–28.

26 Kapikian AZ, Mitchell RH, Chanock RM, Shvedoff RA, Stewart CE. An epidemiology study of altered clinical reactivity to respiratory syncytial (RS) virus infection in children previously vaccinated with an inactivated RSV virus vaccine. *Am. J. Epidemiol.* 1969; **89**: 405–21.

27 Groothuis JR, Levin NJ, Rodriguez W *et al.* Use of intravenous gamma globulin to passively immunize high-risk children against RSV: safety and pharmacokinetics. *Antimicrob. Agents Chemother.* 1991; **35**: 1469–73.

28 Meissner HC, Fulton DR, Groothuis JR *et al.* Controlled trial to evaluate protection of high-risk infants against RSV disease by using standard intravenous immune globulin. *Antimicrob. Agents Chemother.* 1993; **37**: 1655–8.

29 Groothuis JR, Simoes EAF, Levin MJ *et al.* Prophylactic administration of respiratory syncytial virus immune globulin to high-risk infants and young children. *N. Engl. J. Med.* 1993; **329**: 1524–30.

30 The PREVENT Study Group. Reduction of respiratory syncytial virus hospitalization among premature infants and infants with bronchopulmonary dysplasia using respiratory syncytial virus immune globulin prophylaxis. *Pediatrics* 1997; **99**: 93–9.

31 Simoes EAF, Sondheimer H, Top FH Jr *et al.* Respiratory syncytial virus immune globulin for prophylaxis against respiratory syncytial virus disease in infants and children with congenital heart disease. *J. Pediatr.* 1998; **133**: 492–9.

32 Oravax. Oravax Company Press Release, 19 March 1997.

33 Meissner HC, Groothuis JR, Rodriguez WJ *et al.* Safety and pharmacokinetics of an intramuscular monoclonal antibody to RSV (SB 209763) in infants and young children at risk for severe RSV disease. *Antimicrob. Agents Chemother.* 1999; **43**: 1183–8.

34 Johnson S, Pfarr DS, Koenig S *et al.* Comparison of the *in vitro* and *in vivo* activities of two humanized monoclonal antibodies recently tested in phase III clinical trials for the prevention of severe RS disease in high risk children. *17th Annual ESPID Meeting*; 1999 May 19–21; Heraklion, Crete, Greece, 1999; Abstract P-58.

35 Johnson S, Oliver C, Prince GA *et al.* Development of a humanized monoclonal antibody (MEDI-493) with potent *in vitro* and *in vivo* activity against respiratory syncytial virus. *J. Infect. Dis.* 1997; **176**: 1215–24.

36 Subramanian KNS, Weisman LE, Rhodes T *et al.* Safety, tolerance and pharmacokinetics of a humanized monoclonal antibody to respiratory syncytial virus in premature infants and infants with bronchopulmonary dysplasia. *Pediatr. Infect. Dis. J.* 1998; **17**: 110–15.

37 Saez-Llorens X, Castano E, Null D *et al.* Safety and pharmacokinetics of an intramuscular humanized monoclonal antibody to respiratory syncytial virus in premature infants and infants with bronchopulmonary dysplasia. *Pediatr. Infect. Dis. J.* 1998; **17**: 787–91.

38 Abbott Laboratories. Data on file. Abbott Laboratories, International Division, Abbott Park, IL; 2000.

39 Branco L, Johnson LS, Young JF, Tressler R, McCue M, Groothuis JR. Broad-range binding of palivizumab to respiratory syncytial virus (RSV). *17th European Congress of Perinatal Medicine*; 2000 25–28 June; Porto, Portugal; Congress Society; 2000; Abstract p43.

40 Hirsch RL, Tressler R, Sorrentino M *et al.* Synagis® palivizumab humanized monoclonal antibody for protection from RSV lower respiratory tract infection effectively reduces RSV hospitalization in the community. *Fourth International Congress on Pediatric Pulmonology;* 2000 February 21–24; Nice, France. Paris: Èditions EDK; 2000; Abstract D10.

41 Sorrentino M, Powers T. The Palivizumab Outcomes Study Group. Effectiveness of palivizumab: evaluation of outcomes from the 1998–99 respiratory syncytial virus season. *Pediatr. Infect. Dis. J.* 2000; **19**: 1068–71.

42 Cohen AH, Sorrentino M, Powers T. Effectiveness of palivizumab for preventing serious RSV disease. *J. Resp. Dis.* 2000; **2**: S30–2.

43 Groothuis JG, Tressler R. The Expanded Access Study Group. Expanded access study with palivizumab in 1998–99. *Eur. Respir. J.* 2000; **16**: 309.

EXHIBIT 5

J Infect Chemother (2002) 8:201–206
DOI 10.1007/s10156-002-0178-6


REVIEW ARTICLE

Paul Pollack · Jessie R. Groothuis

# Development and use of palivizumab (Synagis): a passive immunoprophylactic agent for RSV

Received: March 5, 2002

**Abstract** Palivizumab (Synagis; Abbott Laboratories), a humanized, monoclonal antibody, prevents lower respiratory tract infection by respiratory syncytial virus (RSV). RSV causes significant morbidity and mortality in young children worldwide and is particularly severe in pre-term infants, children with cardiopulmonary disease, and the immunosuppressed population. The first such genetically engineered agent to be used effectively against a human infectious disease, palivizumab significantly reduces the number of hospitalizations caused by RSV in high-risk infants. This article reviews the preclinical development and clinical experience of palivizumab.

**Key words** Respiratory syncytial virus (RSV) · Bronchiolitis · Chronic lung disease (CLD) · Bronchopulmonary dysplasia (BPD) · Prematurity · Humanized monoclonal antibody · Palivizumab (Synagis) · IMpact-RSV study

## Introduction

Since its initial discovery in chimpanzees and subsequent isolation from children diagnosed with pneumonia and bronchiolitis in the late 1950s, respiratory syncytial virus (RSV) has been implicated as the primary viral etiologic agent in serious lower respiratory tract infections (LRTIs) in infants and young children worldwide.[1] RSV results in significant morbidity and mortality in both developed and developing countries, and is responsible for approximately 4 million deaths annually. Preterm infants are particularly vulnerable to the severe sequelae of RSV infection because of their immature immune and pulmonary systems. Driven by the physical, social, and economic costs of RSV, efforts have been ongoing for over four decades to prevent and treat infections caused by RSV. This article focuses on research advances that have led to the development and use of the humanized monoclonal antibody palivizumab as a means of passive immunoprophylaxis in high-risk preterm infants and children.

P.F. Pollack · J.R. Groothuis
Global Research and Development, Abbott Laboratories, Abbott Park, IL, USA

G.M. Barbarotto (✉)
Medical Communications Associate, Synagis, Dept R4RE Bldg AP34-2, Abbott Laboratories, 200 Abbott Park Road, Abbott Park, IL 60064-6186, USA
Tel. +1-847-935-7565; Fax +1-847-937-2343
e-mail: Gina.Barbarotto@abbott.com

## Rationale for RSV prophylaxis

Respiratory syncytial virus (RSV) is a ubiquitous pathogen. Serologic evidence of infection can be found in nearly all children by age 2 years.[2] RSV in vulnerable populations – premature infants, otherwise healthy infants under age 6 months, and children with chronic lung or heart disease or immunodeficiency – can lead to hospitalization for the administration of supplemental oxygen, intravenous fluids, and/or bronchodilator, antiviral, or corticosteroid medications and mechanical ventilation. Unfortunately, no specific therapy has been proven to be of definitive value in the treatment of this frequently serious illness, and supportive care is all that can be currently offered. Prevention of RSV infection is therefore of primary importance. Hospital infection control practices to avert nosocomial outbreaks are essential, as is parental education regarding disease transmission, recognition of symptoms, and avoidance of factors that increase the risk for infection – day-care attendance, exposure to secondhand smoke, and crowding in the home. Continuing efforts to develop a vaccine against RSV that is both safe and effective have been thwarted by a variety of issues unique to the young infant and to RSV.

## Obstacles to vaccine development

Protection against RSV is vital for premature infants in particular, because these infants lack the maternally ac-

quired passive immunity usually conferred during the last trimester of pregnancy. Infants under 6 months of age would benefit most from vaccination because they tend to develop the most severe illness. Unfortunately, these infants lack an adequately developed immune system to generate an effective immune response upon exposure to antigen introduced via vaccination. Conversely, maternal antibodies to RSV present in full-term infants might neutralize a live, attenuated vaccine before they were able to mount an immune response. A formalin-inactivated vaccine, developed in the 1960s, paradoxically exacerbated pulmonary illness in vaccinated children who were subsequently exposed to wild-type virus in the following RSV season.[3] Serious safety concerns related to this experience persist as vaccine development efforts continue. Furthermore, the existence of two subtypes and multiple strains of RSV, along with the common occurrence of reinfection, would probably require multiple boosters of a vaccine that would have to include multiple subtypes and strains – a technically challenging feat that has yet to be accomplished. Finally, active immunization might interfere with other pediatric vaccinations given in the same time frame.

Success with passive immunoprophylaxis has been greater, although polyclonal immunoglobulin products that preceded the development of palivizumab were either ineffective or had other drawbacks. To adequately protect against RSV infection, an agent has to be effective against both RSV subtypes, A and B, and has to have a reasonable duration of action. In addition, it should be safe and relatively easy to administer. The RSV – hyperimmune globulin (RSV-IGIV, RespiGam, MedImmune, Gaithersburg, MD, USA), required intravenous administration in large volumes. This presented serious obstacles for premature infants with poor intravenous access. In addition, excessive fluid volumes precipitated cardiac complications in some infants.[4] Furthermore, polyclonal, hyperimmune globulins are derived from human blood, thus posing a theoretical risk in terms of infectious disease transmission.

## Background on RSV

Respiratory syncytial virus (RSV) is an RNA virus with a single strand of genetic material encoding for ten proteins. The two most important such proteins, in terms of pathogenicity and immunogenicity, are the F and G glycoproteins located on the viral surface. The G glycoprotein mediates viral attachment to respiratory epithelial cells, while the F (fusion) glycoprotein allows fusion of the viral envelope with the respiratory cell's lipid membrane. It is also responsible for the fusion of adjoining cells to form syncytia, for which the virus is named. While RSV has two subtypes and numerous strains, the F protein is well conserved across all variants, and thus is an ideal target for monoclonal antibody development. Antibody targeted to the highly conserved A epitope of the F protein prevents infection by impeding virus-to-host cell membrane fusion, subsequent cell-to-cell transmission, and viral replication.

## RSV epidemiology and clinical features in Japan

Takeuchi[5] was the first to perform a prospective study to characterize the epidemiologic and clinical features of RSV in Japanese children. In a prospective study of four RSV epidemics, from 1979–1983, he demonstrated that RSV in Japan peaked in December–January, in a finding similar to that of epidemics in other temperate northern hemisphere countries.[5] He also described the clinical characteristics of 124 children hospitalized with RSV disease in Kawasaki Municipal Hospital during the 1982–1983 RSV season. He observed that 78% of the hospitalized patients had evidence of lower respiratory infection and 50% of all hospitalized patients were less than 11 months of age. Takeuchi observed that the clinical features of RSV disease in infants less than 3 months of age often differed from those in older infants. Older infants usually presented with dyspnea, acidosis, and low O2 and high CO2 levels. Three cases of near-miss sudden infant death syndrome (SIDS) were observed in the very young (<3 months) infants; these infants were afebrile throughout their clinical course. Saijo et al.[6] examined a group of 317 Japanese children 13 years of age and younger who were hospitalized for LRTIs between April 1991 and March 1992. The average age of these children was 11 months. Investigators found that 70.5% of the youngest children (<2 years old) and 64.7% of all children tested positive for RSV. RSV accounted for 42.4% of bronchopneumonias, 64.1% of bronchiolitis (all ages), and 74.1% of bronchiolitis in infants under 1 year of age. Similar trends continued in the next RSV season.[7] Overall, 162 children required hospitalization for bronchiolitis before age 3 years. Seventy-six percent were RSV-antigen positive; 43.5% were ≤6 months old. No differences in incidence of RSV were noted between the sexes.

## Long-term sequelae of RSV disease

RSV infection has been associated with long-term pulmonary consequences. The association of early RSV illness with childhood reactive airways disease (RAD/asthma) has been documented in several clinical trials. One such trial, conducted by Sigurs and colleagues,[8] followed 47 infants hospitalized for RSV bronchiolitis and 93 matched controls to the age of 7 in a prospective study. They reported a tenfold increased prevalence of asthma (30% versus 3%; $P < 0.001$) in the infants previously hospitalized with RSV. Such data, suggest that RSV infection at a young age may predispose children to RAD.[8]

## Development of palivizumab

A series of murine monoclonal antibodies was raised against RSV, from which the one with the strongest binding affinity to the F protein was selected. The genes encoding

the complementarity-determining regions (CDRs) were isolated from cells producing that antibody and were incorporated into human genes that encode for the light and heavy chains of a human IgG antibody.[9] IgG was chosen for its long half-life (28 days), which would allow for a convenient monthly dosing schedule throughout the RSV season. The mouse CDRs account for only 5% of the antibody molecule – the remaining 95% is of human origin.

The recombinant genes containing the mouse CDRs and the human immunoglobulin chains were then inserted into a plasmid from *Escherichia coli*. This plasmid was combined with mammalian hybridoma cells, which are immortal in culture and have the ability to produce antibody. A master cell bank was created, from which samples are taken to initiate cultures used in the production of palivizumab. Quality control measures are incorporated throughout the manufacturing process to safeguard against contamination and ensure consistent quality and potency of the product.[9]

## Preclinical studies in the cotton rat

Johnson et al.[10] conducted studies in the cotton rat to determine the biologic properties of this humanized monoclonal antibody. The rats were injected with antibody and the following day were infected intranasally with either RSV subtype A or subtype B.[10] The antibody was effective against both subtypes, resulting in a reduction in viral replication of greater than 99% at an intravenous dose of 2.5 mg/kg. This dose resulted in serum antibody concentrations of around 25–30 μg/ml.[10] This serum concentration was set as the target value to achieve in humans to ensure that the lower respiratory tract was protected against infection with RSV.

Additional studies were conducted to evaluate whether RSV would become more virulent upon primary or secondary challenge in the presence of passively acquired anti-RSV antibody. The concern was whether this antibody, in noninhibitory concentrations, could cause enhanced viral replication or virally mediated pulmonary pathology during primary exposure (reminiscent of the formalin-inactivated virus experience), or permit the development of antibody-resistant strains. There was no increase in viral load or virus-related pulmonary pathology noted upon two challenges. In studies designed to detect antibody-resistant mutants, lung tissue from only one animal that had received a very low dose of antibody (0.0032 mg/kg) grew a single viral plaque. Johnson and colleagues[10] further noted that animals that had been passively immunized were completely resistant to infection after clearance of antibody, suggesting that palivizumab administration does not inhibit a protective immune response to RSV.

In summary, experiments in the cotton rat showed that palivizumab had potent neutralizing and fusion-inhibiting properties for both RSV subtypes A and B, which were dose-dependent. At the same time, it did not enhance viral replication or lung pathology upon subsequent exposure to RSV. The promising results of these studies in the cotton rat were extremely useful in understanding the behavior of RSV virus in the presence of a humanized monoclonal antibody, and paved the way for human studies.

## Clinical trials with palivizumab

The safety and efficacy of palivizumab was investigated in the IMpact-RSV Study.[11] This large ($n = 1502$), multicenter, randomized, double-blind, placebo-controlled, phase III study of children from 139 centers in the United States, United Kingdom, and Canada was conducted during the 1996–1997 RSV season. The primary objective of the study was to determine whether palivizumab would decrease hospitalization rates for premature infants (≤35 weeks' gestation and ≤6 months of age) and for children up to 2 years old with active bronchopulmonary dysplasia (BPD) requiring treatment within the past 6 months. Subjects received either 15 mg/kg palivizumab or placebo intramuscularly (IM) once a month for 5 months during the RSV season. Excluded from the study were those children who were expected to require prolonged hospitalization (>30 days), those who required mechanical ventilation, had a history of current or previous RSV infection, or hepatic, congenital heart, or renal disease, seizure disorder, history of immunodeficiency or an allergy to IgG, had received RSV-related vaccine products (such as RSV-IVIG), and/or who had a life expectancy of less than 6 months. Secondary study endpoints are listed in Table 1.

In the IMpact-RSV study, 500 children were randomized to the placebo group and 1002 to receive palivizumab. The two groups were well-matched for sex, race, weight, age, and number of people in the household, birth weight, number of weeks' gestation, incidence of multiple births, whether there were other children in the home, presence in day care, and family history of atopy.

A total of 1486 children (99% of participants) completed the study. There was an overall 55% ($P < 0.001$) reduction in hospitalization for the palivizumab group; the placebo group had a hospitalization rate of 10.6% and the palivizumab group's hospitalization rate was 4.8%. Significant reductions were also observed in subsets of the investigational population. Preterm infants without BPD born between 32 and 35 weeks' gestation had an 82% reduction in hospitalization, from 10.0% to 1.8%. A 39% reduction in

**Table 1.** Primary and secondary endpoints of the IMpact-RSV study[11]

*Primary*
- Hospitalization with confirmed case of RSV

*Secondary*
- Incidence of hospitalizations
- Total number of days in hospital
- Total number of days requiring supplemental oxygen
- Total number of days with moderate to severe lower respiratory tract illness (LRI score = 3)
- Total number of days spent in the intensive care unit
- Total number of days necessitating mechanical ventilation
- Incidence of otitis media

RSV, Respiratory syncytial virus; LRI, lower respiratory tract infection

hospitalization rates, from 12.8% to 7.9%, was noted for infants with BPD. With the exception of otitis media, all secondary endpoints were achieved. Statistically significant reductions were observed in intensive care unit (ICU) admissions, total hospitalizations, and those related to respiratory illness, numbers of days in the hospital, days of required oxygen administration, and days with moderate to severe LRTI. Adverse events were rare, and were comparable in both the palivizumab and placebo groups, and none were judged to be medication-related. This phase III investigation concluded that palivizumab was effective, safe, and well tolerated.

## Pharmacokinetic and safety bridging studies

Bridging studies were conducted to determine whether the safety and efficacy of palivizumab established in the IMpact-RSV study would be observed in the Japanese population. In a phase I safety trial, palivizumab was given to six Japanese and six overseas healthy adult volunteers to evaluate dose, safety, and pharmacokinetics. The dosages evaluated were 3mg/kg IM, 3mg/kg intravenous (IV), 10mg/kg IV, and 15mg/kg IV. The larger doses were administered IV because of the large volumes required. No significant differences were found between the Japanese and overseas groups in terms of maximum concentrations, area under the curve (AUC), half-life, clearance, and trough concentrations.[12] No adverse reactions were observed. Phase II bridging studies were subsequently conducted in Japanese children. Thirty-one children (19 preterm, 13 with BPD (also known as chronic lung disease), were given 15mg/kg of palivizumab IM. There were no significant differences in mean serum trough palivizumab levels, serum concentrations, and AUC between the Japanese and overseas children, nor were any adverse reactions reported. One child developed a mild RSV upper respiratory tract infection (URI), which did not require hospitalization.[12]

Over 700 RSV isolates from both subtypes A and B from 19 countries have been tested for palivizumab binding. These included 23 isolates (13 A strains and 10 B strains) from Japan. All isolates from all countries were successfully bound by palivizumab.[11]

## Post-licensing clinical experience

Based on the results of the IMpact-RSV study, palivizumab was approved for use in 1998 in the United States and in 1999 in Europe. Palivizumab received regulatory approval in Japan in February 2002.

Since 1998, phase IV trials have examined RSV hospitalization rates for preterm children with and without BPD in the presence or absence of prophylaxis with palivizumab. Simoes and Groothuis[13] performed a metaanalysis of 18 of these studies, which were conducted in the United States, United Kingdom, Canada, France, the Netherlands, and other European Union countries. Prospective and retrospective and comparative and noncomparative studies were included. Children were divided into three subgroups: children less than age 2 years with chronic lung disease (CLD), children born at 29–32 weeks' gestational age without CLD, and children born at 32–35 weeks' gestational age without CLD. Hospitalization rates were computed by dividing the total number of subjects with one or more RSV-related hospitalizations by the total number of subjects in the study.

The study found that nonprophylaxed and palivizumab-prophylaxed RSV hospitalization rates were 17.9% and 5.6%, respectively, in the CLD children, 10.2% and 2.0%, respectively, for children born at 29–32 weeks' gestational age, and 9.8% and 1.5%, respectively, for children born at 32–35 weeks' gestational age. These findings provide strong support for the use of palivizumab in high-risk infants and children (Table 2).

### Surveillance data regarding tolerance and adverse events

Postmarketing pharmacovigilance has not identified any serious adverse events among recipients of palivizumab beyond those identified in the IMpact-RSV study. Approximately 272879 patient exposures to palivizumab occurred between October 1998 and June 2001. None of the 121 deaths in these patients were attributed to palivizumab. The incidence of mild or moderate adverse events, including upper respiratory tract infection, otitis media, rhinitis, fever, rash, cough, diarrhea, wheeze, nervousness, or bronchiolitis ranged from 0.3% to 5.8%, as reported by physicians administering the injection and through telephone contact with parents of recipients, respectively. Serious adverse events, such as dyspnea, asthma, pneumonia, and fever, occurred in only 0.1% of the group reported on by physicians and in 2.8% of the group contacted by telephone.[13] No serious injection-site reactions, such as muscular atrophy or contracture, have been reported.

## Summary

Respiratory syncytial virus (RSV) is one of the most important causes of lower respiratory tract illness in infants and children worldwide and causes significant morbidity, particularly for preterm infants and those with cardiac, pulmonary, and immunodeficiency states. Prevention is vital for those at greatest risk. Palivizumab is currently the only proven and licensed prophylaxis against lower respiratory tract infection caused by RSV. Randomized clinical trials and outcomes surveys support its effectiveness and safety in reducing RSV-related hospitalization rates in high-risk infants. Palivizumab may be given in an outpatient setting via the intramuscular route once per month during the RSV season. Its convenient route of administration and good tolerability profile enhance compliance with this monthly

**Table 2.** Combined analysis of prophylaxed and nonprophylaxed children in three subgroups: (1) BPD/CLD, less than 2 years of age; (2) 29–32 weeks' gestational age (wGA) without CLD; and (3) 32–35 wGA without CLD

**Infants with BPD/CLD <2 years of age ($n$ = 3675)**

| Study (country) | RSV hospitalization rates | | | |
|---|---|---|---|---|
| | Unprophylaxed patients | | Palivizumab patients | |
| | Rate | ($n$) | Rate | ($n$) |
| Groothuis (USA)[14] | 36.7% | (30) | | |
| PREVENT (USA)[15] | 17.4% | (149) | | |
| Stevens et al. (USA)[16] | 25.2% | (131) | | |
| Greenough et al. (UK)[17] | 19.1% | (235) | | |
| IMpact-RSV (USA/Can/UK)[11] | 12.8% | (266) | 7.9% | (496) |
| Outcomes 1998–1999 (USA)[18] | | | 4.0% | (402) |
| Outcomes 1999–2000 (USA)[19] | | | 3.9% | (795) |
| COMPOSS (Canada)[20] | | | 6.0% | (95) |
| PharmaScope (NL)[21] | | | 3.4% | (88) |
| ATU (France)[22] | | | 7.6% | (506) |
| Registry 2000–2001[23] | | | 5.8% | (482) |
| **Weighted mean rate** | **18.4%** | **(811)** | **5.6%** | **(2864)** |

**Infants 29–32 wGA without CLD ($n$ = 4854)**

| Study (country) | RSV hospitalization rates | | | |
|---|---|---|---|---|
| | Unprophylaxed patients | | Palivizumab patients | |
| | Rate | ($n$) | Rate | ($n$) |
| IRIS 1 (Spain)[24] | 10.1% | (456) | | |
| IRIS 2 (Spain)[25] | 12.9% | (827) | | |
| Stevens et al. (USA)[16] | 7.6% | (662) | | |
| IMpact-RSV (US/Can/UK)[11] | 8.5% | (142) | 1.6% | (313) |
| Outcomes 1998–1999 (USA)[18] | | | 2.0% | (506) |
| Outcomes 1999–2000 (USA)[19] | | | 2.3% | (690) |
| COMPOSS (Canada)[20] | | | 1.3% | (199) |
| PharmaScope (NL)[21] | | | 0.8% | (124) |
| Registry 2000–2001 (USA)[23] | | | 2.3% | (650) |
| International Study W00-355[26] | | | 2.1% | (285) |
| **Weighted mean rate** | **10.3%** | **(2087)** | **2.0%** | **(2767)** |

**Infants 32–35 wGA without CLD ($n$ = 2829)**

| Study (country) | RSV hospitalization rates | | | |
|---|---|---|---|---|
| | Unprophylaxed patients | | Palivizumab patients | |
| | Rate | ($n$) | Rate | ($n$) |
| IMpact-RSV (USA/Can/UK)[11] | 9.8% | (123) | 2.0% | (250) |
| Outcomes 1998–1999 (USA)[18] | | | 1.5% | (548) |
| Outcomes 1999–2000 (USA)[19] | | | 1.3% | (972) |
| Registry 2000–2001 (USA)[23] | | | 1.6% | (936) |
| **Weighted Mean Rate** | **9.8%** | **(123)** | **1.5%** | **(2706)** |

BPD, Bronchopulmonary dysplasia; CLD, chronic lung disease; RSV, respiratory syncytial virus
Reprinted from *Respiratory Medicine*, volume no. 96, Supplement B; Simoes EAF and Groothuis JR: "Respiratory syncytial virus prophylaxis. The story so far." Pages S16–S25, 2002, by permission of the publisher WB Saunders

regimen. Recent bridging studies have demonstrated that palivizumab has identical pharmacokinetics and safety profiles in high-risk Japanes and Caucasian children, and guidelines for its use have been dev loped.

**Acknowledgments** We would like to gratefully acknowledge Wendy Horn for drafting the manuscript and Stacy Simpson and Gina M. Barbarotto for editing and technical assistance.

## References


1. Garenne M, Ronsmans C, Campbell H. The magnitude of mortality from acute upper respiratory infections in children under 5 years in developing countries. World Health Statist Q 1992;45:180–91.
2. Glezen WP, Taber LH, Frank AL, Kasel JA. Risk of primary infection and reinfection with respiratory syncytial virus. Am J Dis Child 1986;140:543–6.
3. Kapikian AZ, Mitchell RH, Chanock RM, Shvedoff RA, Stewart CE. An epidemiology study of altered clinical reactivity to respiratory syncytial (RS) virus infection in children previously vaccinated with an inactivated RSV virus vaccine. Am J Epidemiol 1969;89:405–21.
4. Simoes EAF, Sondheimer H, Top FH Jr, Meissner HC, Welliver RC, Kramer AA, et al. Respiratory syncytial virus immune globulin for prophylaxis against respiratory syncytial virus disease in infants and children with congenital heart disease. J Pediatr 1998;133:492–9.
5. Takeuchi Y. Epidemiological and clinical features of influenza and respiratory syncytial virus infections among children in Japan. Acta Paediatr Jpn 1988;30:231–9.
6. Saijo M, Ishii T, Kokubo M, Takimoto M, Takahashi Y. Respiratory syncytial virus infection in lower respiratory tract and asthma attack in hospitalized children in North Hokkaido, Japan. Acta Paediatr Jpn 1993;35:233–7.
7. Saijo M, Takahashi S, Kokubo M, Saino T, In-Yaku F, Ishii T, et al. The role of respiratory syncytial virus in acute bronchiolitis in small children in northern Japan. Acta Paediatr Jpn 1994;36:371–4.
8. Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B. Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7. Am J Respir Crit Care Med 2000;161:1501–7.
9. Young J. Development of a potent respiratory syncytial virus-specific monoclonal antibody for the prevention of serious lower respiratory tract disease in infants. Respir Med 2002;96(Suppl B): S31–5.
10. Johnson S, Oliver C, Prince GA, Hemming VG, Pfarr Ds, Wang SC, et al. Development of a humanized monoclonal antibody (MED-493) with potent in vitro and in vivo activity against respiratory syncytial virus. J Infect Dis 1997;176:1215–24.
11. The IMpact-RSV Study Group. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. Pediatrics 1998;102:531–7.
12. Groothuis JR, Nishida H. Prevention of respiratory syncytial virus infections in high-risk infants by monoclonal antibody (palivizumab). Pediatr Int 2002;44:235–41.
13. Simoes EAF, Groothuis JR. Respiratory synctytial virus prophylaxis. The story so far. Respir Med 2002;96(Suppl B):S16–25.
14. Groothuis JR, Simoes EAF, Levin MJ, Hall CB, Long CE, Rodriguez WJ, et al. Prophylactic administration of respiratory syncytial virus immune globulin to high-risk infants and young children. N Engl J Med 1993;329:1524–30.
15. The PREVENT Study Group. Reduction of respiratory syncytial virus hospitalization among premature infants with bronchopulmonary dysplasia using respiratory syncytial virus immune globulin prophylaxis. Pediatrics 1997;99:93–9.
16. Stevens TP, Sinkin RA, Hall CB, Maniscalco WM, McConnochie KM. Respiratory syncytial virus and premature infants born at 32 weeks' gestation or earlier: hospitalization and economic implications of prophylaxis. Arch Pediatr Adolesc Med 2000;154:55–61.
17. Greenough A, Cox S, Alexander J, Lenney W, Turnbull F, Burgess S, et al. Health care utilisation of infants with chronic lung disease, related to hospitalisation for RSV infection. Arch Dis Child 2001;85:463–8.
18. Sorrentino M, Powers T, and the Palivizumab Outcomes Study Group. Effectiveness of palivizumab: evaluation of outcomes from the 1998 to 1999 respiratory syncytial virus season. Pediatr Infect Dis J 2000;19:1068–71.
19. Cohen AH, Sorrentino M, Powers T. Effectiveness of palivizumab for preventing serious RSV disease. J Respir Dis 2002;2(Suppl): S30–2.
20. Oh PI, Lanctôt KL, Yoon A, Lee DSC, Paes BA, Simmons BS, et al. Prophylaxis for respiratory syncytial virus in Canada: outcomes and utilization with palivizumab during the 1999–2000 season. Pediatr Infect Dis J 2002;21:512–8.
21. van Kan CI, Eenhoorn PC, Zweens MJ, Woltil HA, Baarsma R. Palivizumab surveillance: an evaluation of RSV-related hospitalization of high-risk children after palivizumab prophylaxis in The Netherlands during the 1999–2000 RSV season. Abstract presented at Fifth World Congress of Perinatal Medicine, 23–27 September 2001, Barcelona, Spain.
22. Lacaze-Masmonteil T, Rozé J-C, Fauroux B, and the French pediatricians group of the Synagis patients' name based program. Incidence of respiratory syncytial virus-related hospitalizations in high-risk children: follow-up of a palivizumab-prophylaxed cohort. Pediatr Pulmonol 2002 in press.
23. Hand I, Boron M, Van Veldhuisen P, for the Synagis Outcomes Registry. Synagis (palivizumab) prophylaxis of respiratory syncytial virus (RSV) infection. Patient demographics and preliminary results from the 2000–2001 Synagis Outcomes Registry. Poster for Abstract #1714, presented at the Fifth World Congress of Prerinatal Medicine, 23–27 September 2001, Barcelona, Spain.
24. Carbonell-Estrany X, Quero J, Bustos G, Cotero A, Domenech E, Figueras-Aloy J, et al. Rehospitalization because of respiratory syncytial virus infection in premature infants younger than 33 weeks of gestation: a prospective study. Pediatr Infect Dis J 2000;19:592–7.
25. Carbonell-Estrany X, Quero J, and the IRIS Study Group. RSV hospitalization rates in premature infants born over two consecutive seasons. Pediatr Infect Dis J 2001:20:874–9.
26. Grässl G, Andreou A, Pinquier D, Maragliano G, Lagercrantz H, Guimaraes H, et al. Efficacy and safety of palivizumab (Synagis) in preterm infants 29–32 weeks gestational age without chronic lung disease to prevent serious respiratory syncytial virus respiratory tract infection. Abstract presented at the Fifth World Congress of Perinatal Medicine, 23–27 September 2001, Barcelona, Spain.

# ABSTRACT OF THE DISCLOSURE

A human-murine neutralizing antibody against respiratory syncytial virus which is specific for respiratory syncytial virus F protein. Such an antibody is useful for preventing or treating respiratory syncytial virus infection.